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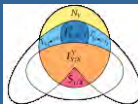
Terzolas (TN), Italy - 27.6.2019

Information-Theoretic Analysis of Brain and Physiological Networks: *Applications*

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University of Palermo, Italy



OUTLINE

- **INTRODUCTION**

- Information Dynamics
- Network Physiology: different contexts

- **APPLICATIONS: PHYSIOLOGICAL NETWORKS**

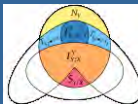
- Networks of cardiovascular interactions
- Networks of cardiorespiratory interactions
- Networks of cerebrovascular interactions

- **APPLICATIONS: BRAIN-BODY AND BRAIN-HEART INTERACTIONS**

- Brain-heart and brain-brain interactions during sleep
- Brain-body interactions during mental stress
- Brain-heart interactions during emotion elicitation
- Brain-heart interactions in epilepsy

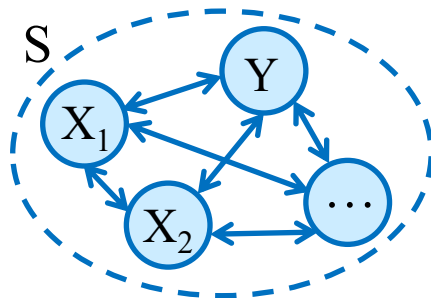
- **APPLICATIONS: SINGLE ORGAN NETWORKS**

- Brain Networks from EEG recordings
- Muscle Networks probed during postural control

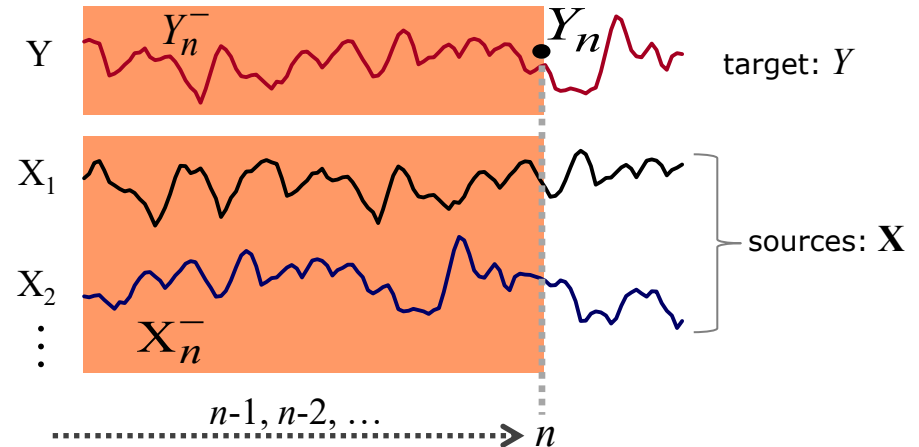


INFORMATION DYNAMICS IN NETWORKS OF DYNAMICAL SYSTEMS

- Dynamical System $S = \{Y, X_1, X_2, \dots\}$

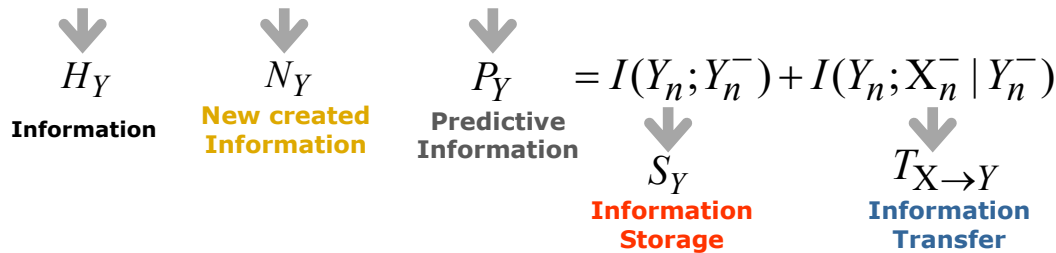


- Dynamic Process $S = \{Y, X_1, X_2, \dots\}$



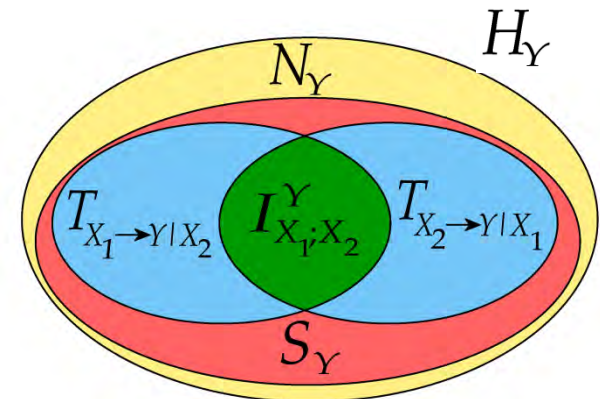
Information Decomposition

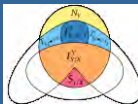
$$H(Y_n) = H(Y_n | X_n^-, Y_n^-) + I(Y_n; X_n^-, Y_n^-)$$



$$T_{X \rightarrow Y} = T_{X_1 \rightarrow Y | X_2} + T_{X_2 \rightarrow Y | X_1} + I_{X_1; X_2}^Y$$

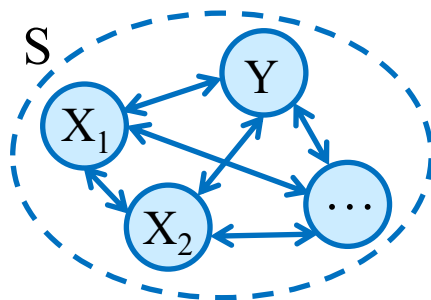
Joint information Transfer
 Individual information Transfer
 Interaction Transfer



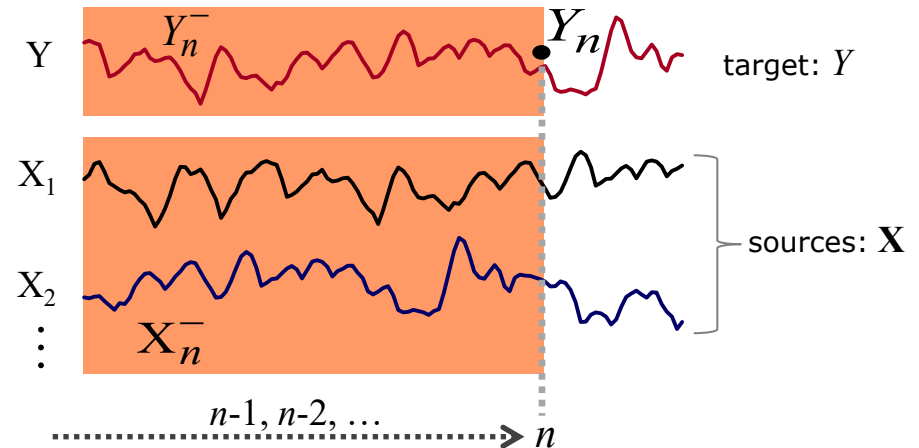


INFORMATION DYNAMICS IN NETWORKS OF DYNAMICAL SYSTEMS

- Dynamical System $S = \{Y, X_1, X_2, \dots\}$

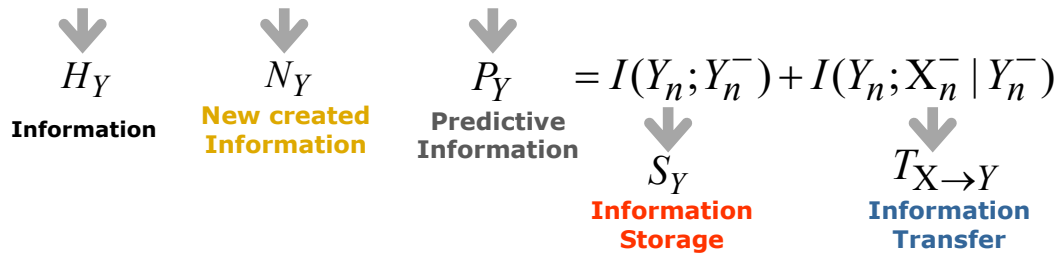


- Dynamic Process $S = \{Y, X_1, X_2, \dots\}$



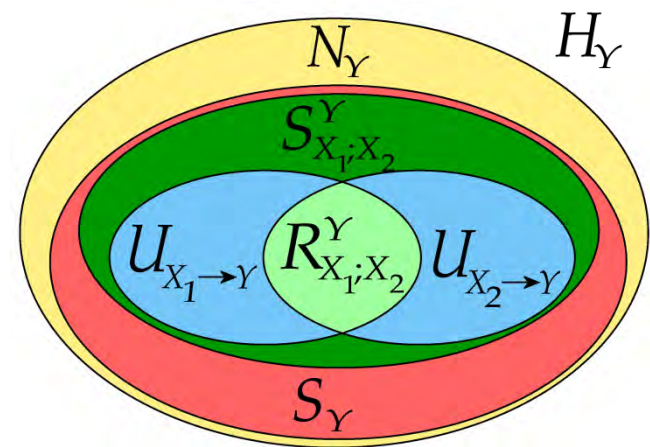
Information Decomposition

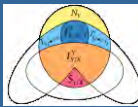
$$H(Y_n) = H(Y_n | X_n^-, Y_n^-) + I(Y_n; X_n^-, Y_n^-)$$



$$T_{X \rightarrow Y} = U_{X_1 \rightarrow Y} + U_{X_2 \rightarrow Y} + R_{X_1; X_2}^Y + S_{X_1; X_2}^Y$$

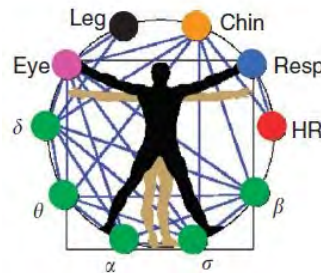
\downarrow \downarrow \downarrow \downarrow
 Joint information Transfer Unique information Transfer Redundant Transfer Synergistic Transfer





NETWORK PHYSIOLOGY

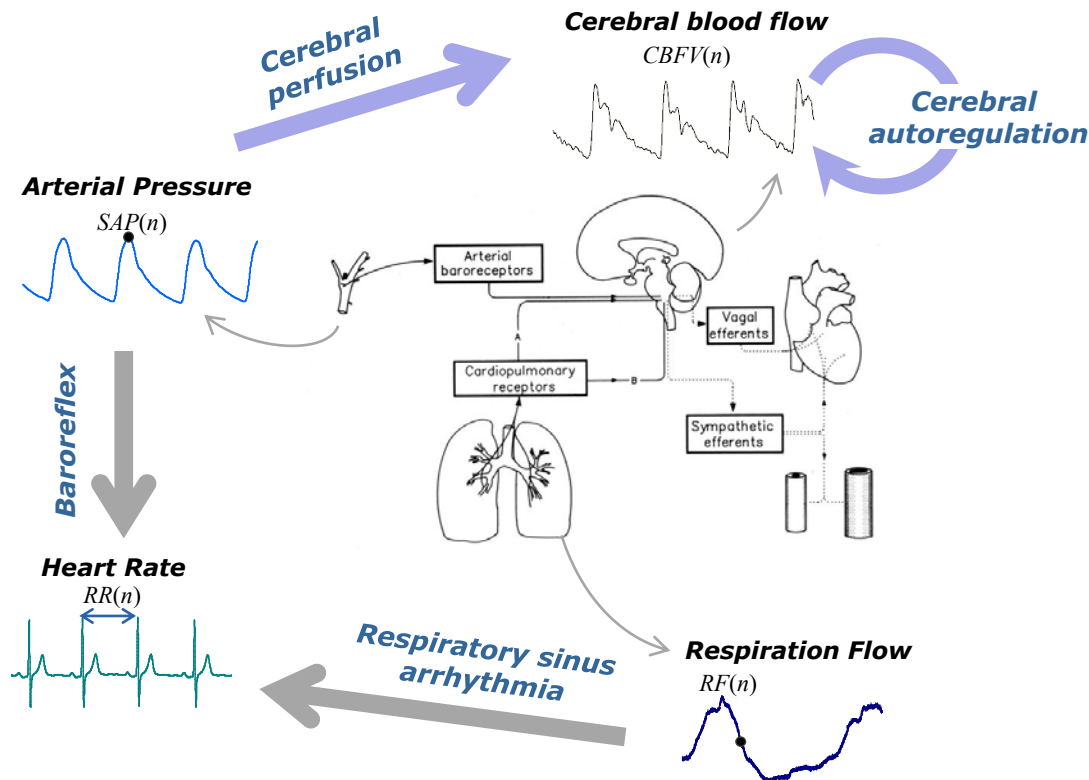
- **NETWORK PHYSIOLOGY:**
[Bashan A et al., Nature Comm 2012]

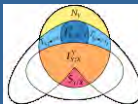


Organ systems exhibit a degree of activity and interactivity depending on the physiological state

- **PHYSIOLOGICAL NETWORKS**

Network of physiological interactions (cardiovascular, cardiorespiratory, cerebrovascular)





BRAIN-BODY AND BRAIN-HEART INTERACTIONS

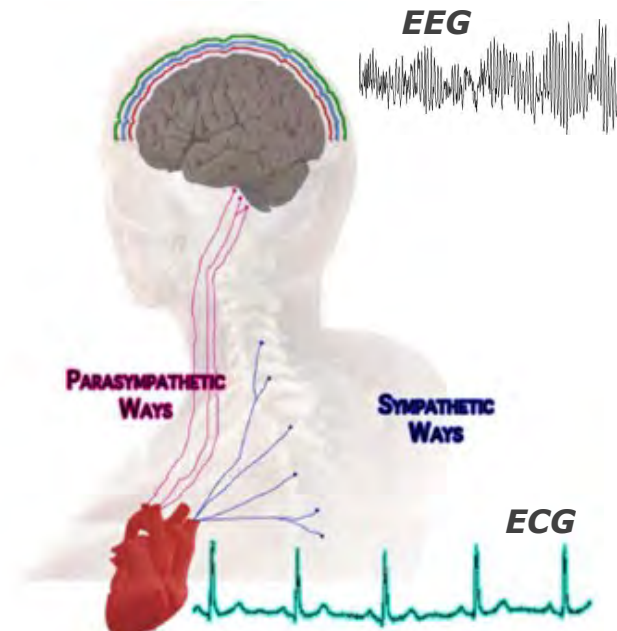
- **Brain-body interactions:**

- common patterns of neural activity in the central and peripheral nervous systems which reflect the coordination between brain and body
- These patterns can be probed by simultaneous measures of brain and organ activity

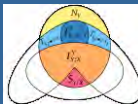


- **Brain-heart interactions:**

- relate cardiac physiology with central and peripheral nervous system activity
- Simultaneous brain-heart recordings may explain how cardiovascular arousal can influence physiological states or cognitive functions



Information flow in large-scale networks of brain-body interactions allows to establish the integration of **efferent commands** from brain to body and **afferent feedback** from body to brain

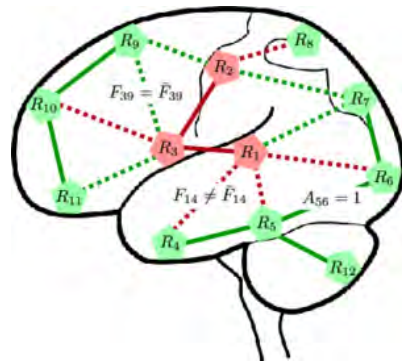


SINGLE-ORGAN NETWORKS

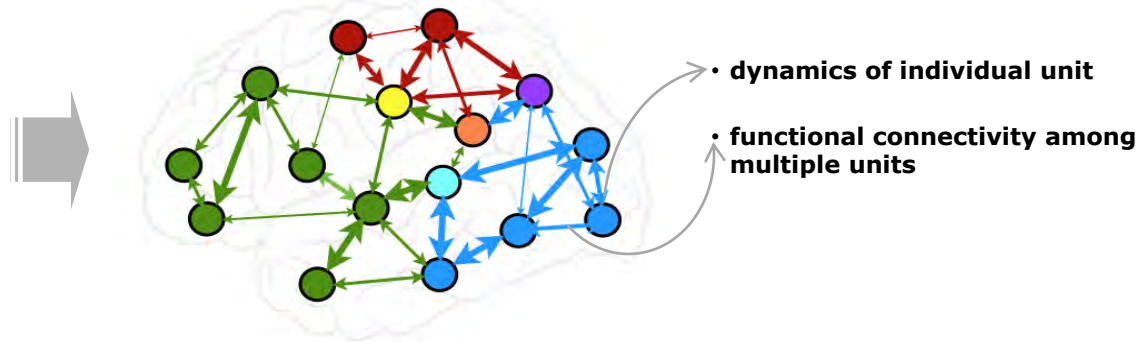
- **BRAIN NETWORKS:** functional networks probed studying EEG from multiple brain regions

Segregation and integration: spatially distributed specialized brain areas are functionally connected

[G. Tononi et al, PNAS 1994]

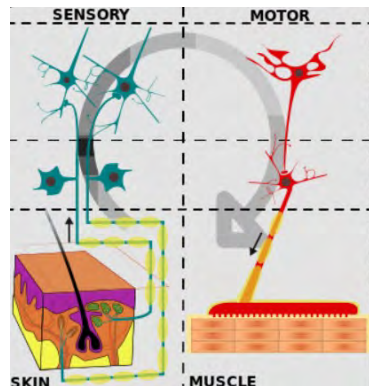


distributed brain dynamics

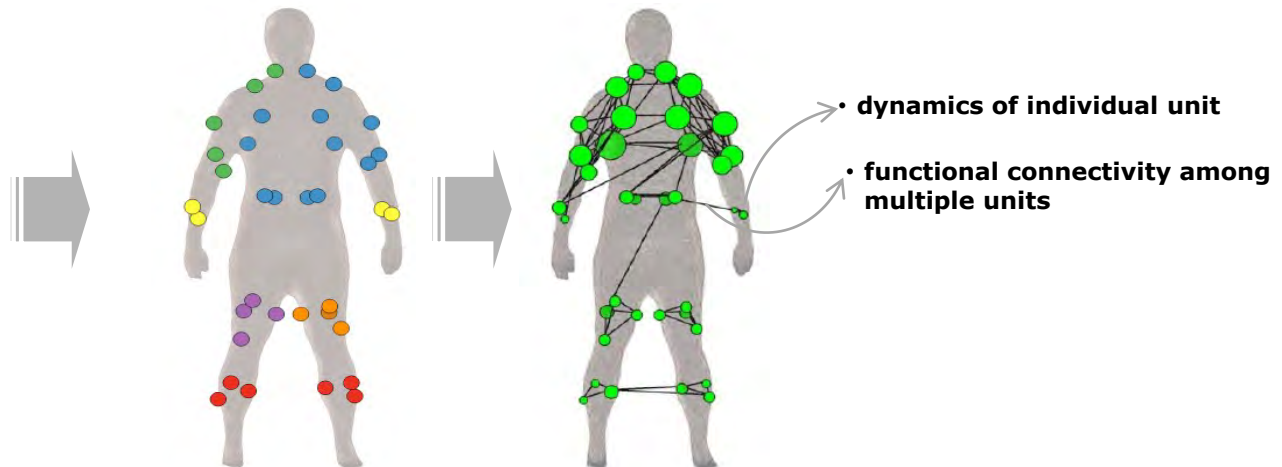


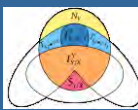
- **MUSCLE NETWORKS:** functional networks probed studying EMG recorded from multiple muscles distributed across the body

[T.W. Boonstra et al, Sci Rep 2015]



distributed muscular dynamics

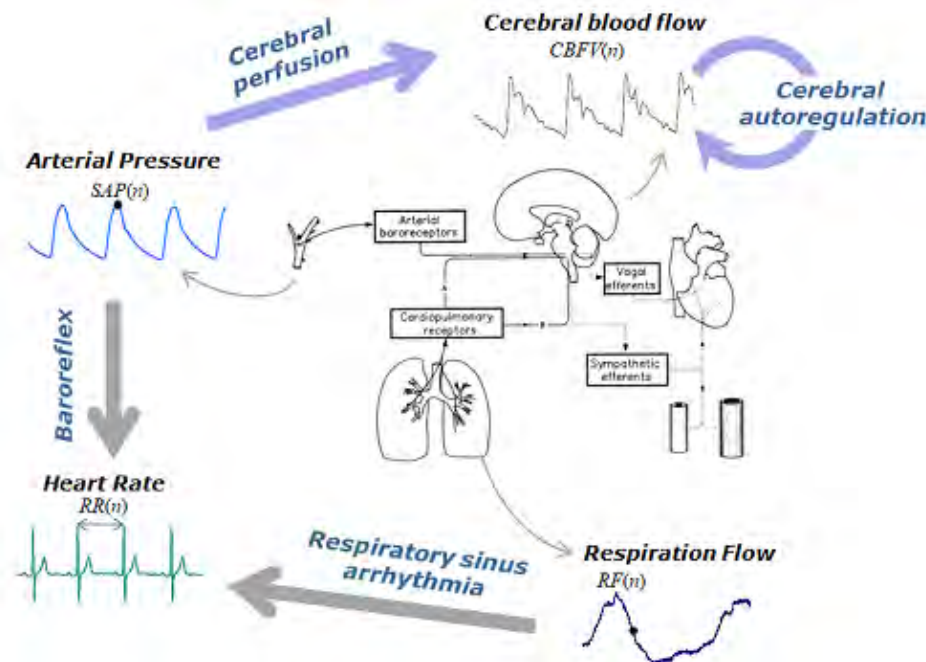


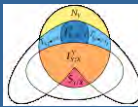


APPLICATIONS: PHYSIOLOGICAL NETWORKS

- Networks of cardiovascular interactions
- Networks of cardiorespiratory interactions
- Networks of cerebrovascular interactions

Network of *cardiovascular, cardiorespiratory and cerebrovascular* short-term physiological interactions

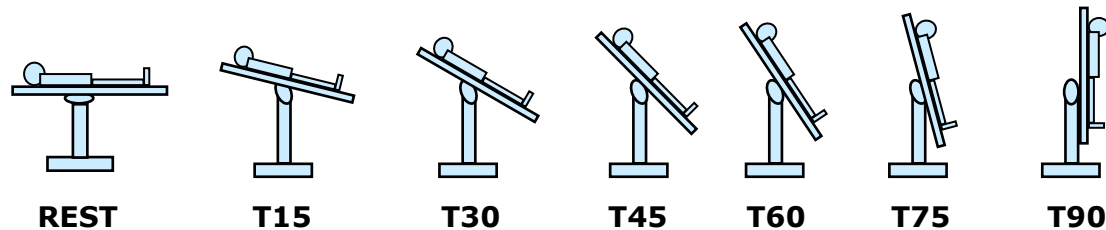




Applications: Complexity of the CARDIAC CONTROL

Graded Head-up tilt protocol

17 young healthy subjects



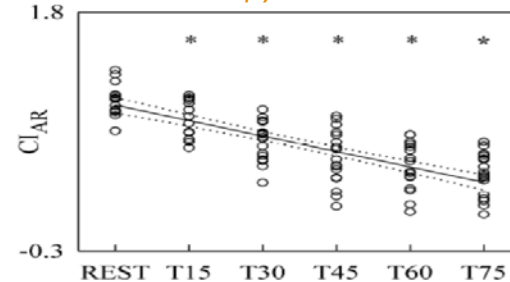
- The dynamical complexity of short-term heart period variability decreases progressively with tilt-table angle

- Linear estimator
- Univariate analysis

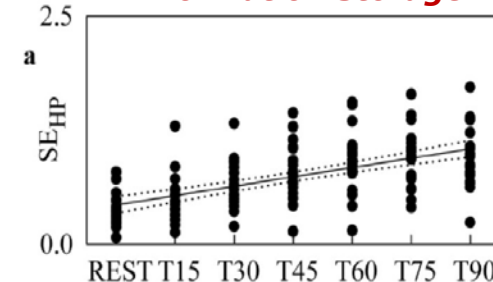
New Information N_Y

Information Storage S_Y

Conditional Entropy = New Information

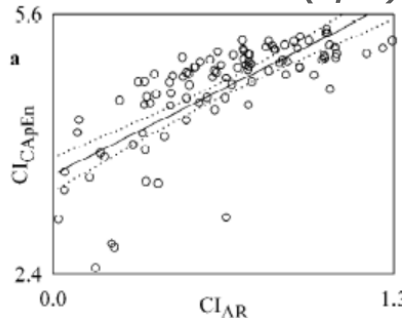


Information Storage

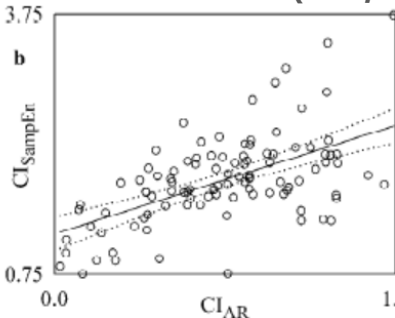


- Complexity assessed by linear model-based estimators significantly correlates with model-free estimates

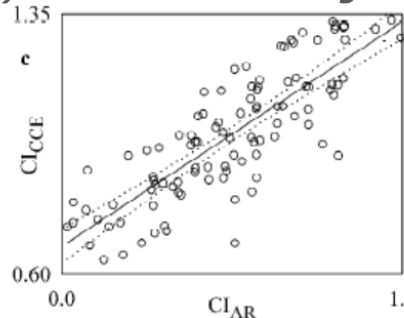
Linear vs. Kernel (ApEn)



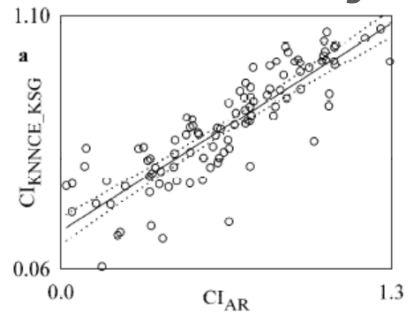
Linear vs. Kernel (SampEn)

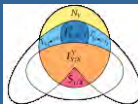


Linear vs. binning



Linear vs. nearest neighbors

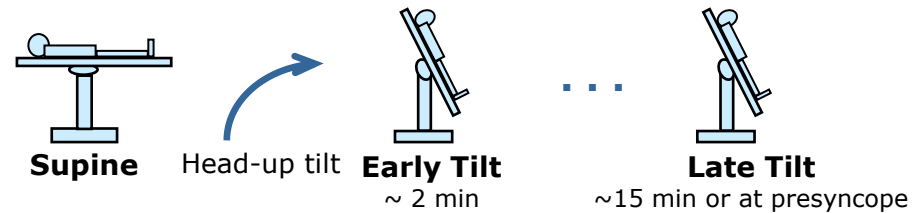




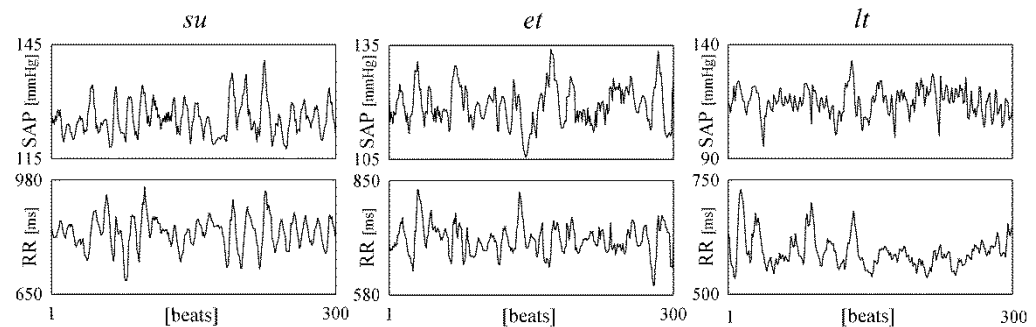
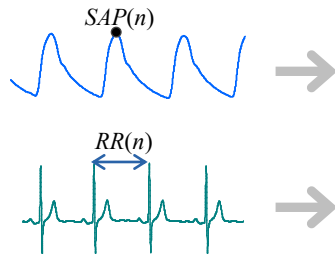
Applications: CARDIOVASCULAR INTERACTIONS

Protocol:

- **Subjects with postural-related syncope**
- **Healthy controls**



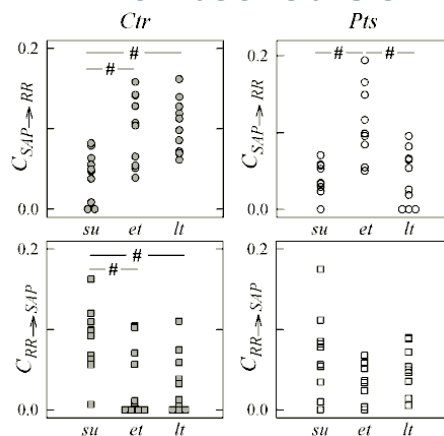
Measured Time series:



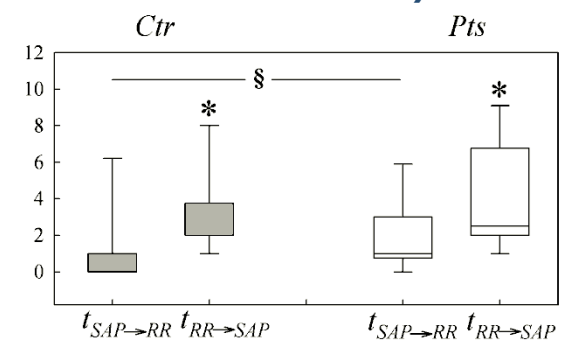
- **Binning estimator with NUE**
- **Bivariate analysis**

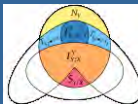
Information Transfer $T_{X \rightarrow Y}$
 $T_{Y \rightarrow X}$

Information transfer



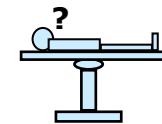
Interaction delays



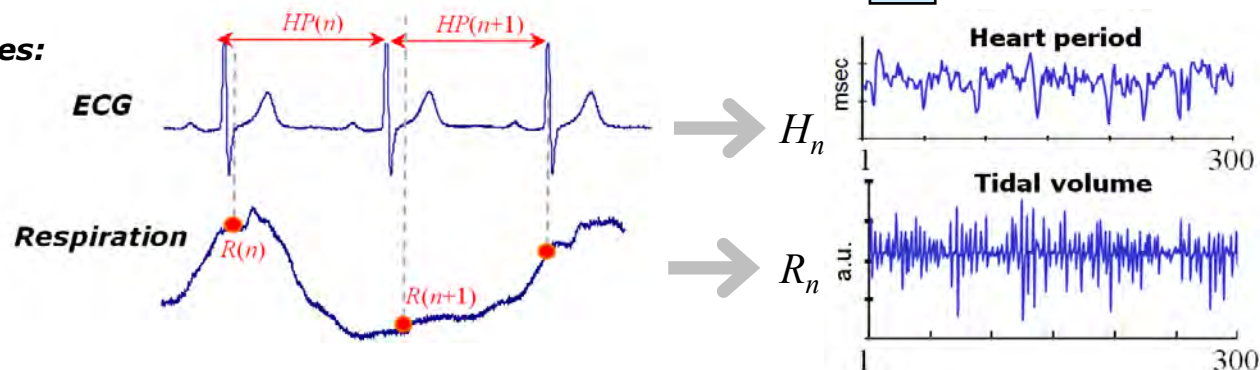


Applications: CARDIORESPIRATORY INTERACTIONS

- **Protocol:** healthy subjects during attention and mental stress tasks



- **Measured time series:**



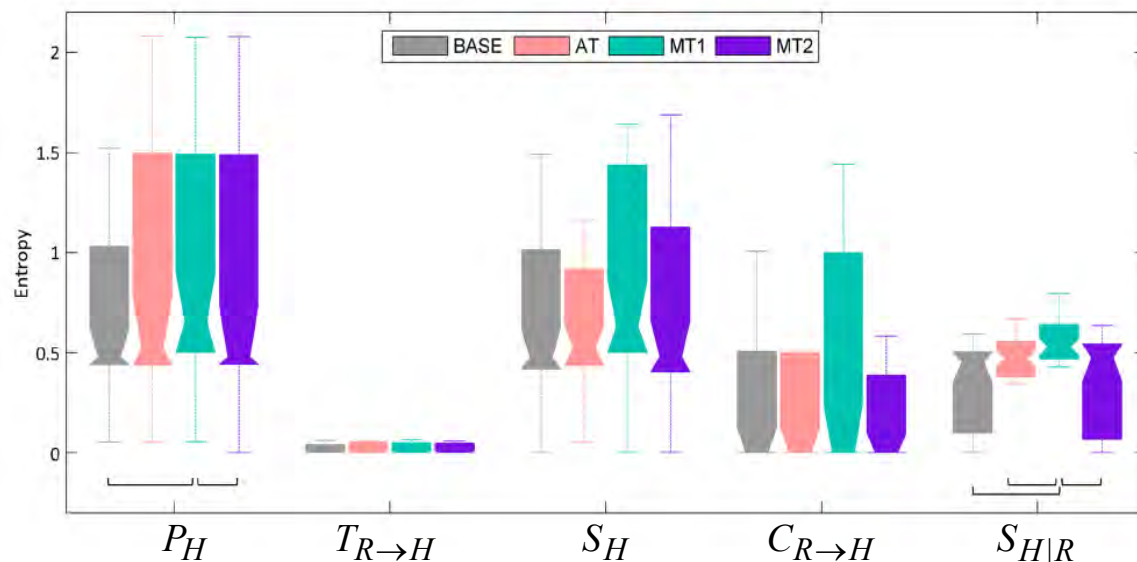
- **Binning estimator with NUE**
- **Bivariate analysis**

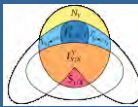
$$P_Y = S_Y + T_{X \rightarrow Y}$$

$$= C_{X \rightarrow Y} + S_{Y|X}$$

Predictive Information, Information Storage and Information Transfer are not informative about mental stress

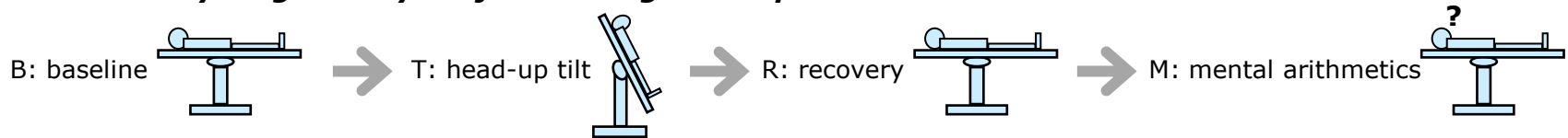
Internal Information
measured by conditional self-entropy is higher during mental stress





Applications: CARDIOVASCULAR and CARDIORESPIRATORY INTERACTIONS

- Protocol: 61 young healthy subjects during head-up tilt and mental stress tasks**

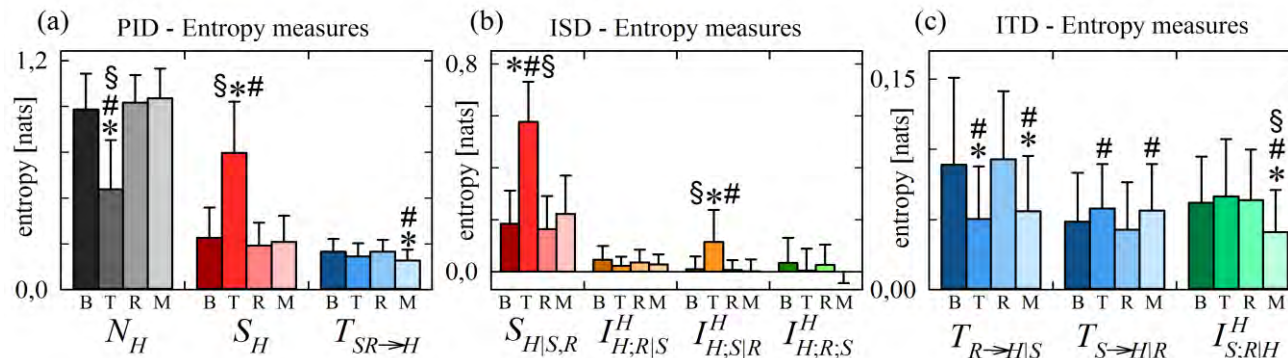
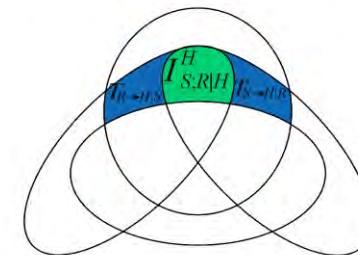
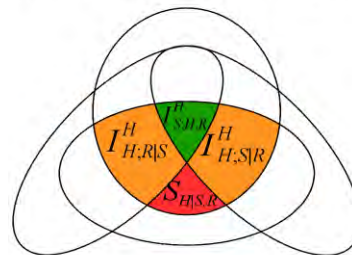
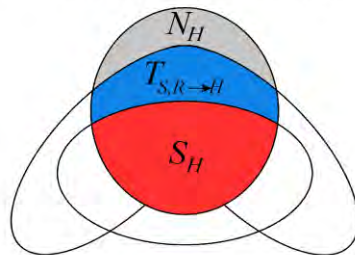


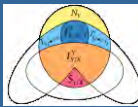
- Measured time series:** Heart period (H), systolic arterial pressure (S), respiration (R) – 300 points in each condition
- Linear estimator**
- Network analysis** – full information decomposition: $H_Y = N_Y + S_Y + T_{X \rightarrow Y} = N_Y + S_{Y|X} + I_{Y;X}^Y + T_{X_1 \rightarrow Y|X_2} + T_{X_2 \rightarrow Y|X_1} + I_{X_1;X_2}^Y$

Predictive Information Decomposition

Information Storage Decomposition

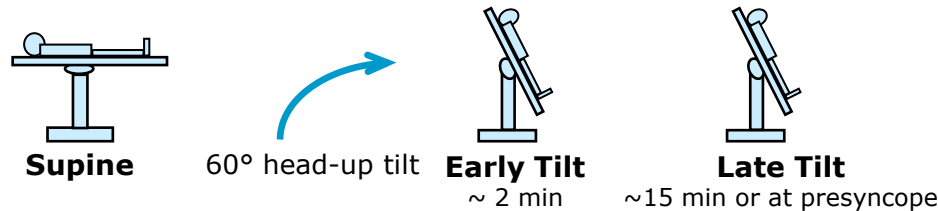
Information Transfer Decomposition



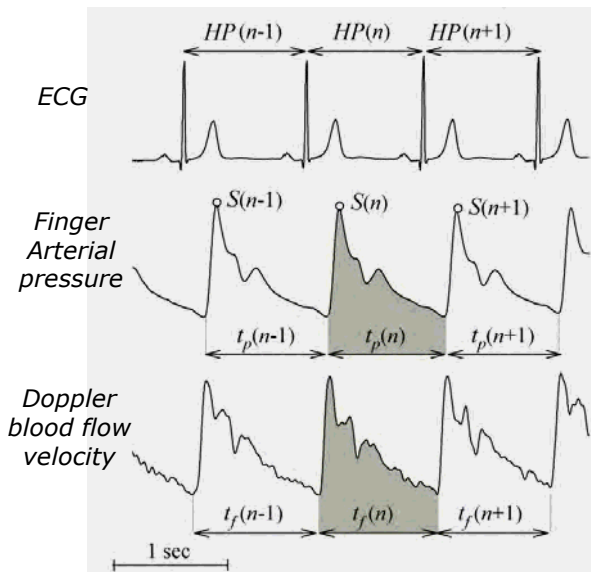


Applications: CARDIOVASCULAR AND CEREBROVASCULAR INTERACTIONS

- Protocol: 10 subjects with postural-related syncope**

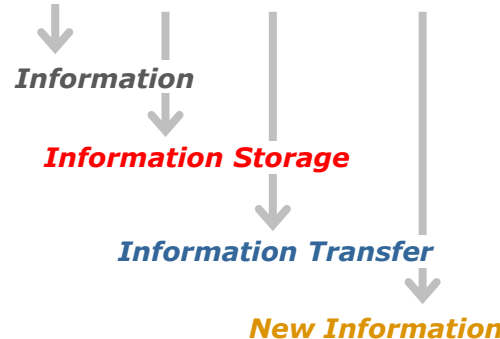


- Signals and time series**

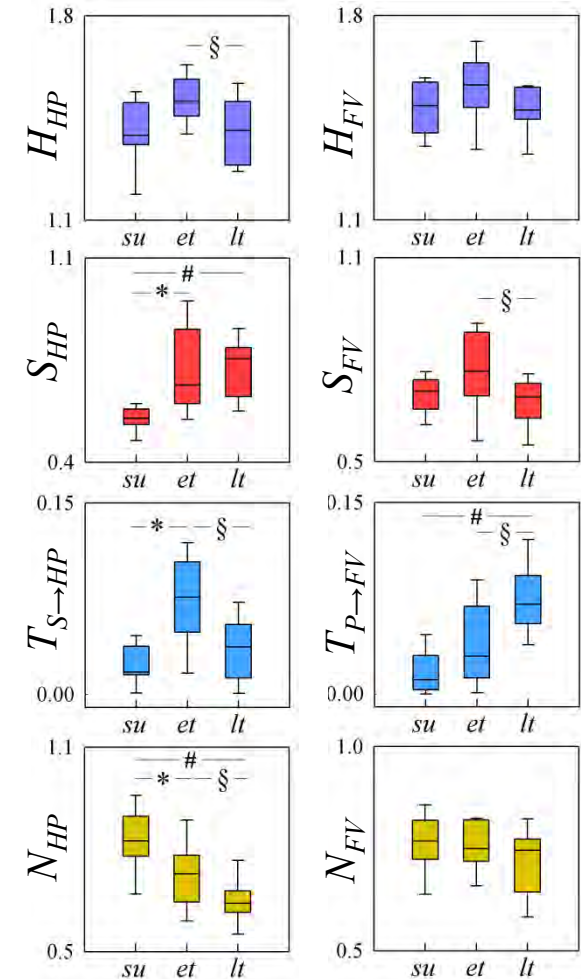


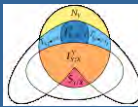
- Binning estimator with NUE
 - Bivariate analysis, **target HP or FV**
- Entropy decomposition:

$$H_Y = S_Y + T_{X \rightarrow Y} + N_Y$$



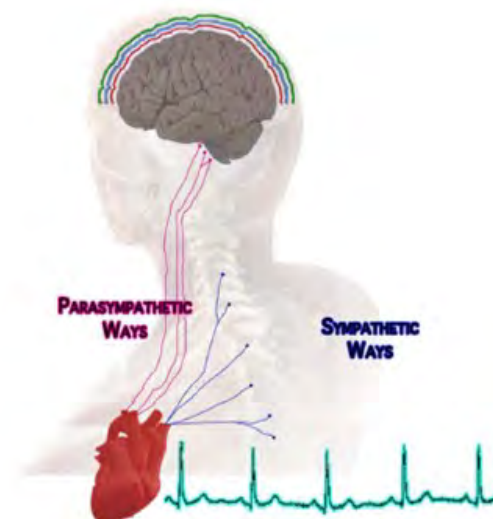
- Results**

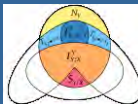




APPLICATIONS: BRAIN-BODY AND BRAIN-HEART INTERACTIONS

- Brain-heart and brain-brain interactions during sleep
- Brain-body interactions during mental stress
- Brain-heart interactions during emotion elicitation
- Brain-heart interactions in epilepsy





(1) BRAIN-BRAIN AND BRAIN-HEART INTERACTIONS DURING SLEEP

• Network of physiological interactions during sleep:

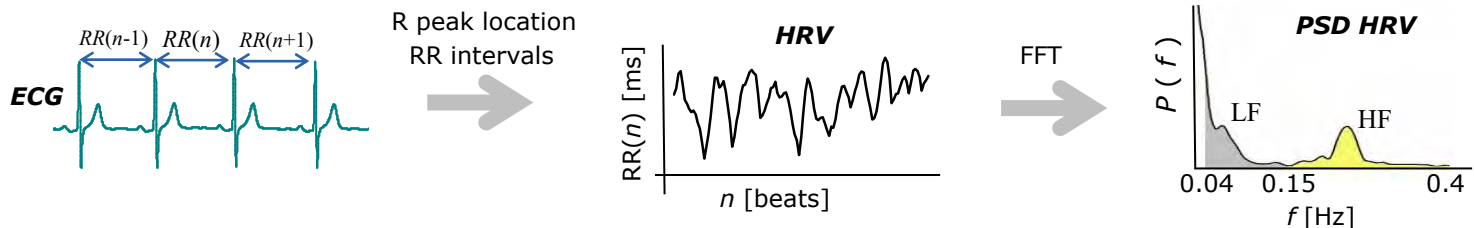
- Spectral analysis of EEG activity



Brain wave amplitudes:

$$P_{\delta}, P_{\theta}, P_{\alpha}, P_{\sigma}, P_{\beta}$$

- Spectral analysis of heart rate variability (HRV)



- Depth of sleep is related to ANS activity, and is reflected in EEG and HRV spectra

• LIGHT Sleep

- ↓ sympathetic activity
- ↑ parasympathetic activity

$$\uparrow P_{\delta} \quad \uparrow P_{HF}$$

• DEEP Sleep

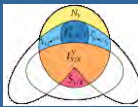
- ↓↓ sympathetic activity

$$\uparrow\uparrow P_{\delta} \quad \uparrow\uparrow P_{HF}$$

• REM Sleep

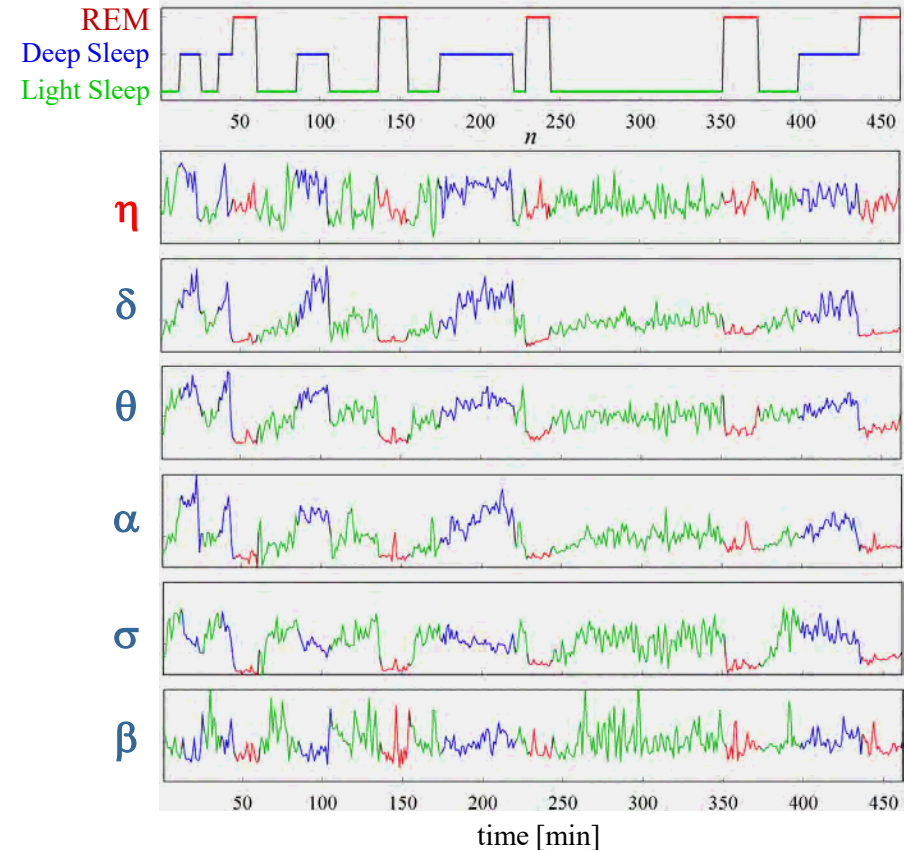
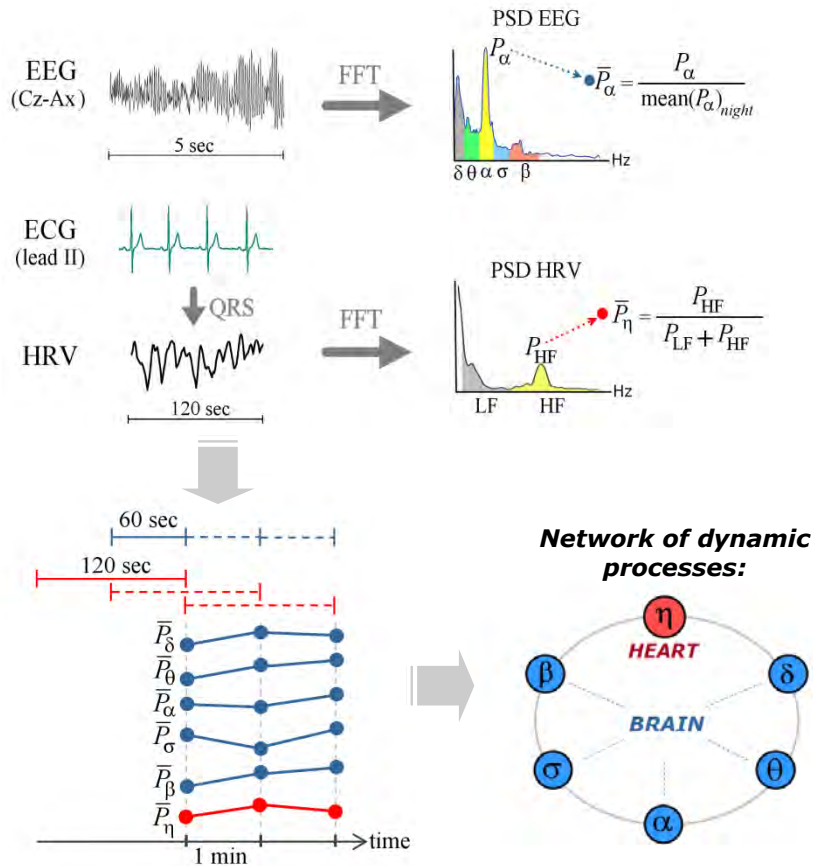
- ↑ sympathetic activity
- ↓ parasympathetic activity

$$\downarrow P_{\delta} \quad \downarrow P_{HF}$$



Brain-heart and brain-brain interactions during sleep: **PROTOCOL**

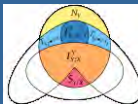
- **Protocol:** full night polysomnography in 10 healthy subjects monitored during sleep
- **Signals and measurement:**
- **Time series:**



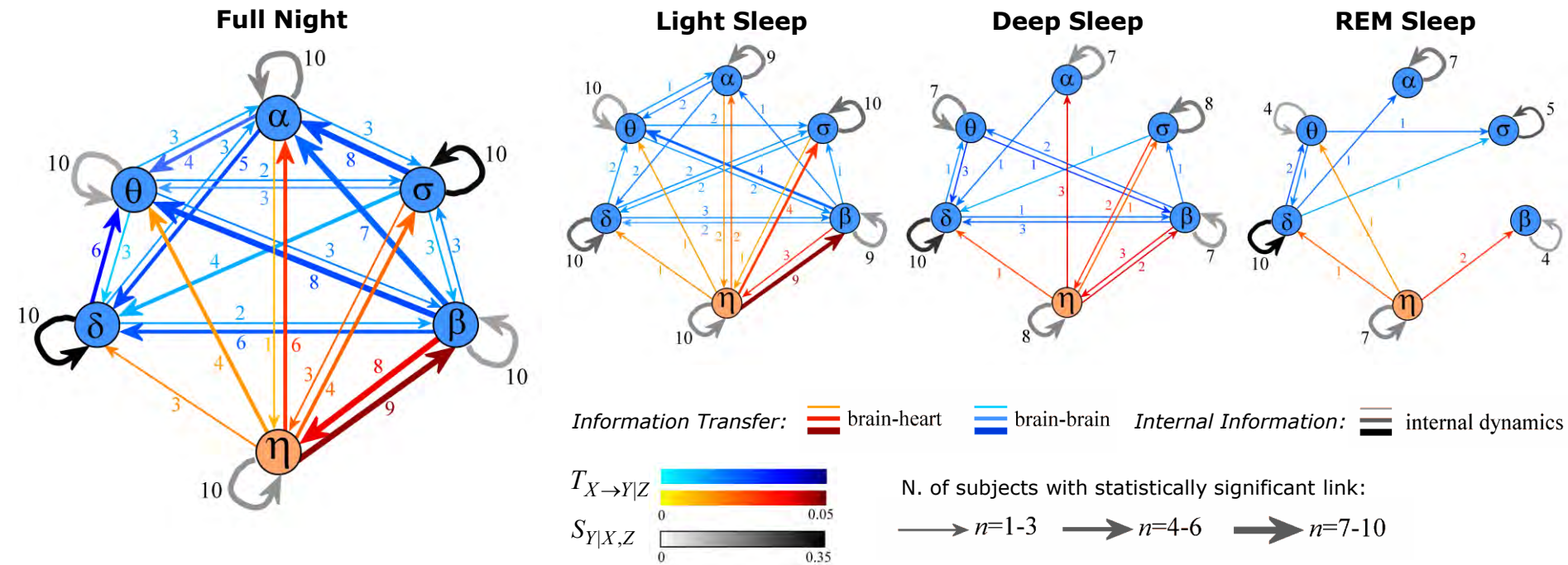
- **Network analysis**

Linear estimator: • Conditional information transfer: $T_{X \rightarrow Y|Z}$
Statistical significance assessed by F-test

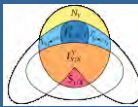
• Internal information storage: $S_{Y|X,Z}$



Brain-heart and brain-brain interactions during sleep: RESULTS

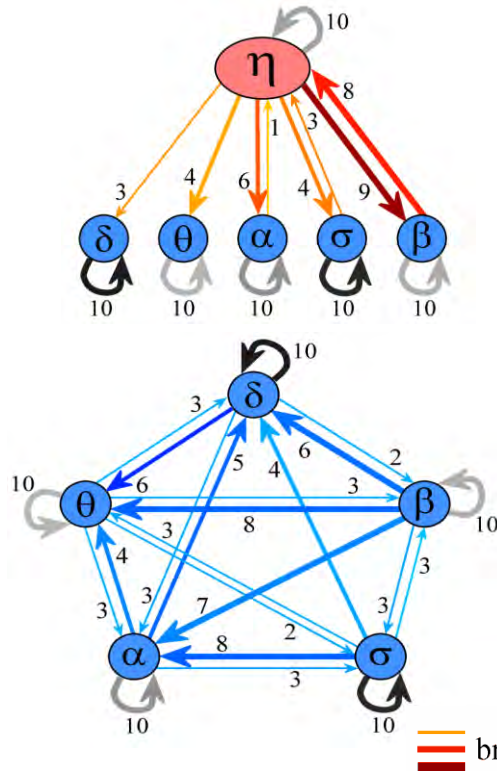


Structured brain-heart and brain-brain network, with the EEG β wave acting as network hub
The interaction network is sustained by the sleep stage transitions

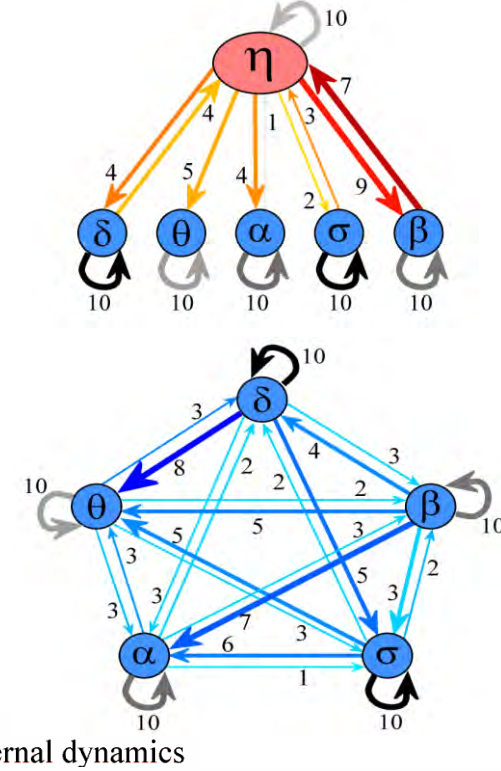


Brain-heart and brain-brain interactions during sleep: RESULTS

MODEL-BASED ANALYSIS (linear estimator)



MODEL-FREE ANALYSIS (kNN estimator)



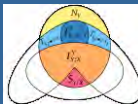
number of subjects with statistically significant PTE or cSE (F-test): $\longrightarrow n=1-3$ $\longrightarrow n=4-6$ $\longrightarrow n=7-10$

Common traits:

- Brain - heart interactions:** Bidirectional between HF_n and EEG β wave
- Brain - brain interactions:** Fully connected network with transfer mostly from β, σ towards δ, θ, α
- Internal dynamics:** Strong self-dependencies in all rhythms

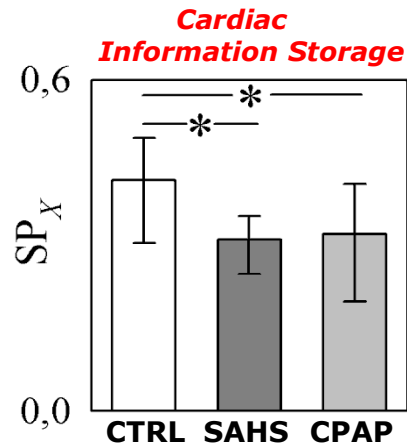
Different traits:

- The δ EEG rhythm shows a significantly higher number of outgoing nonlinear links**

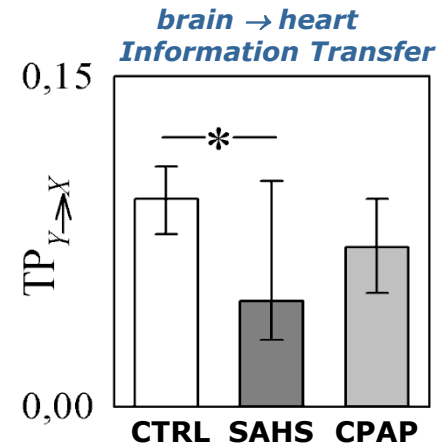


Brain-heart and brain-brain interactions IN SLEEP APNEAS

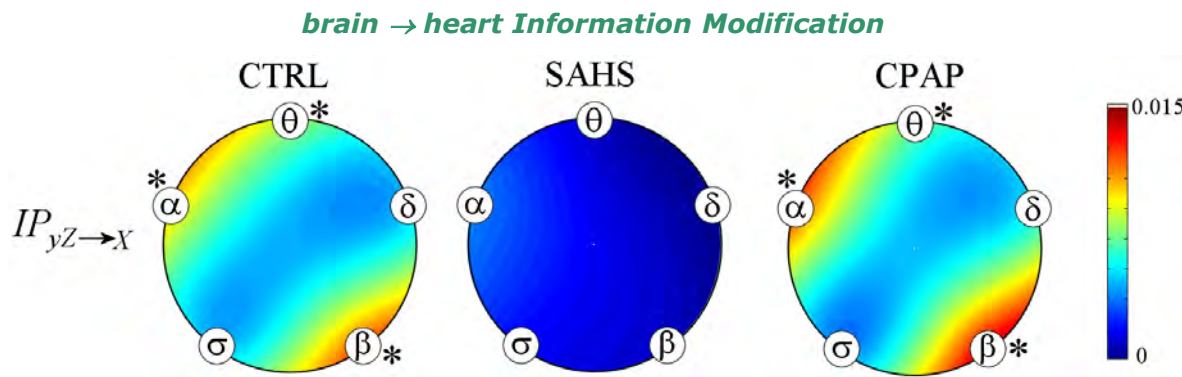
- ✓ 8 sleep apnoea-hypopnoea patients **SAHS**
- ✓ same patients after continuous positive airway pressure therapy **CPAP**
- ✓ 14 healthy controls **CTRL**



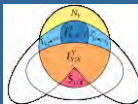
Cardiac dynamics are more complex during sleep apneas, with no recovery after treatment



brain → heart causal interactions are impaired by sleep apneas, and partially restored by CPAP therapy



Redundancy is a feature of undisturbed sleep, lost in SAHS and recovered by treatment



(2) BRAIN-BODY INTERACTIONS DURING STRESS

- Goal:** to quantify how central and peripheral nervous system functionally interact in resting states and during altered states
- Protocol:** recording of multiple physiological signals through wearable multisensor devices

- ✓ 18 healthy subjects
- ✓ Experimental protocol:

rest phase (12 min)



mental arithmetic (7 min)

368 + 311 =

rest phase (12 min)



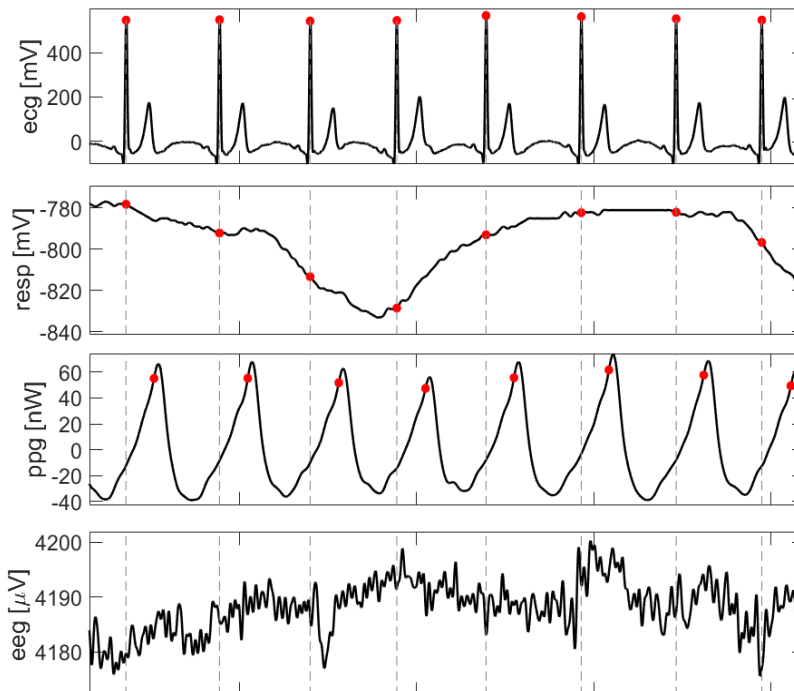
serious game (7 min)



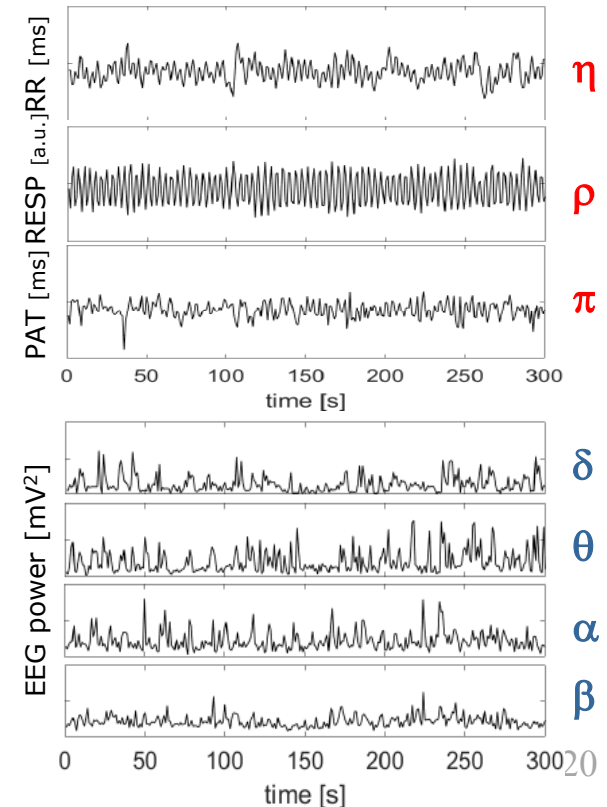
Devices:



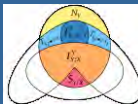
Signals and measurement:

RR
intervalsRESP
amplitudePulse
Arrival
TimePSD
EEG

Time series:

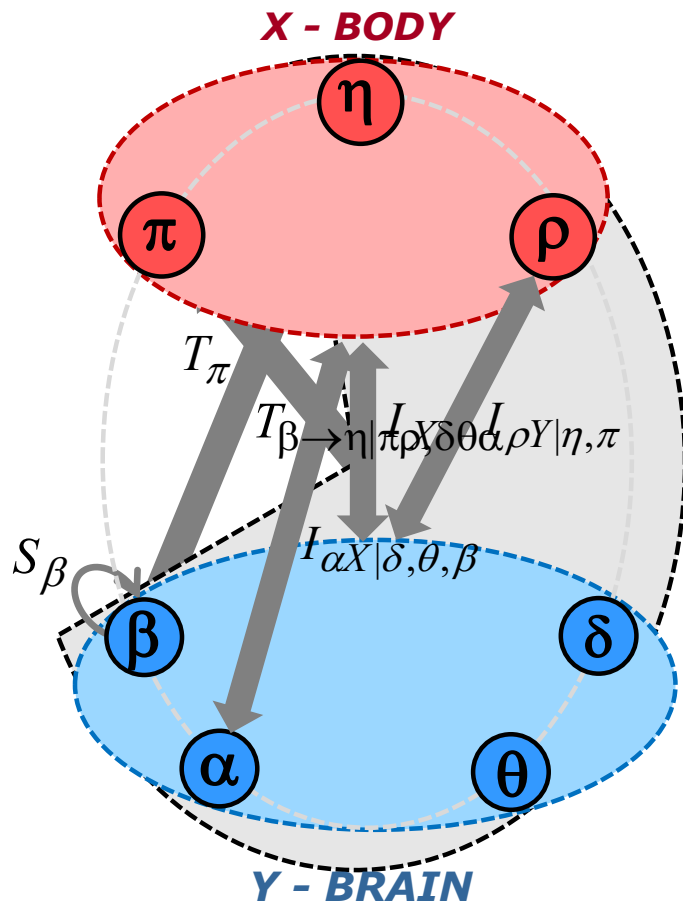
 η ρ π δ θ α β

20



Brain-body interactions during stress: MEASURES

- NETWORK REPRESENTATION:** $N = \{S_1, \dots, S_7\} = \{X, Y\}$ $X = \{\eta, \rho, \pi\}$, $Y = \{\delta, \theta, \alpha, \beta\}$



- NETWORK MEASURES:**

Mutual information (static) measures

Brain-Body Mutual Information:

$$I_{XY} = I(X_n; Y_n)$$

Mutual Information between brain and single body node:

$$I_{X_i Y | X^i} = I(X_{i,n}; Y_n | X_n^i) \quad i = 1, 2, 3$$

Mutual Information between body and single brain node:

$$I_{Y_j X | Y^j} = I(Y_{j,n}; X_n | Y_n^j) \quad j = 1, 2, 3, 4$$

Measures of Information Dynamics

Information Storage:

$$S_i = I(S_{i,n}; S_{i,n}^-) \quad i = 1, \dots, 7$$

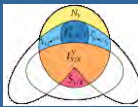
Total Information Transfer:

$$T_j = I(S_{j,n}; S_n^{j-} | S_{j,n}^-) \quad j = 1, \dots, 7$$

Conditional Information Transfer:

$$T_{i \rightarrow j | k} = I(S_{j,n}; S_{i,n}^- | S_n^{i-}) \quad i, j = 1, \dots, 7$$

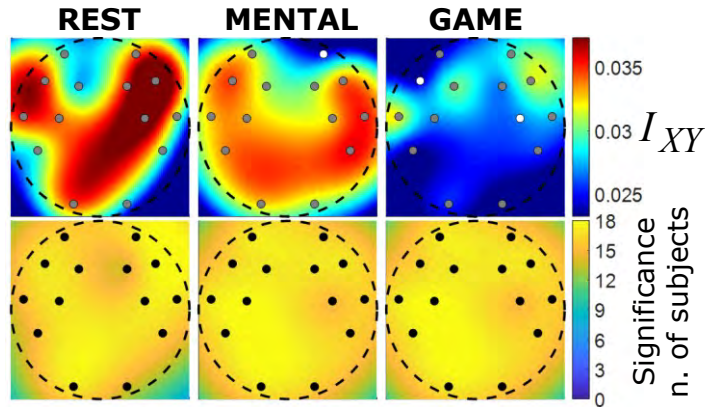
- Analysis: linear estimator;** statistical significance assessed by F-test



Brain-body interactions during stress: RESULTS

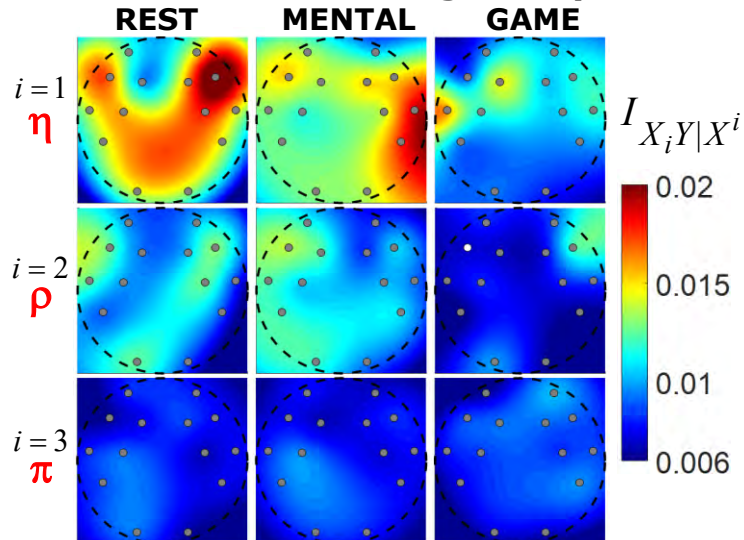
• Static analysis > Mutual Information

Global brain-body MI

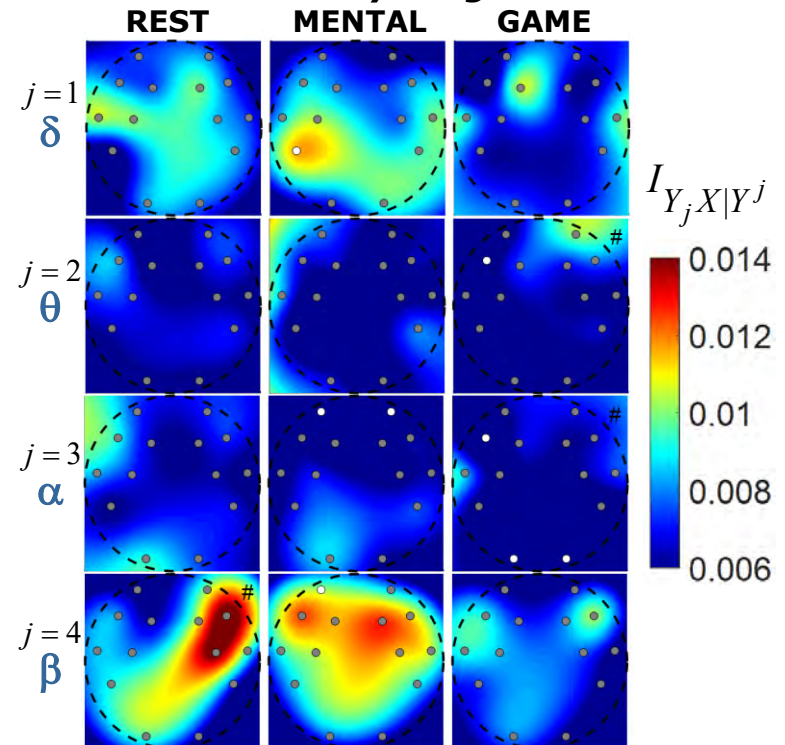


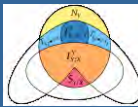
- *brain and body communicate mainly through the heart rhythm and the beta wave activity*
- *The brain-heart communication is weakened during sustained attention evoked by serious game playing*

Conditional MI brain-single body node



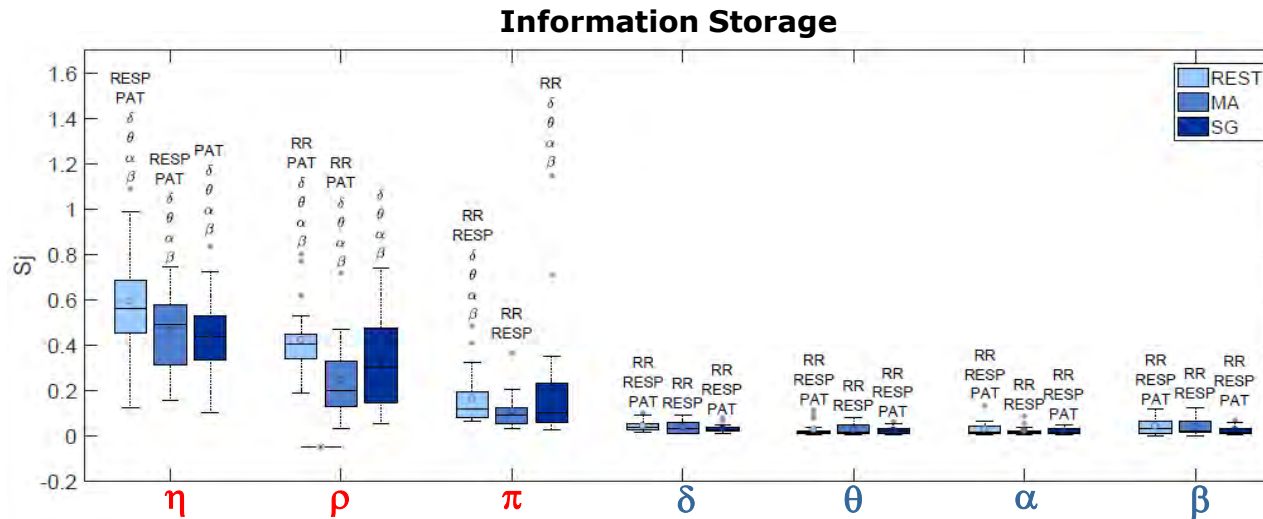
Conditional MI body-single brain node



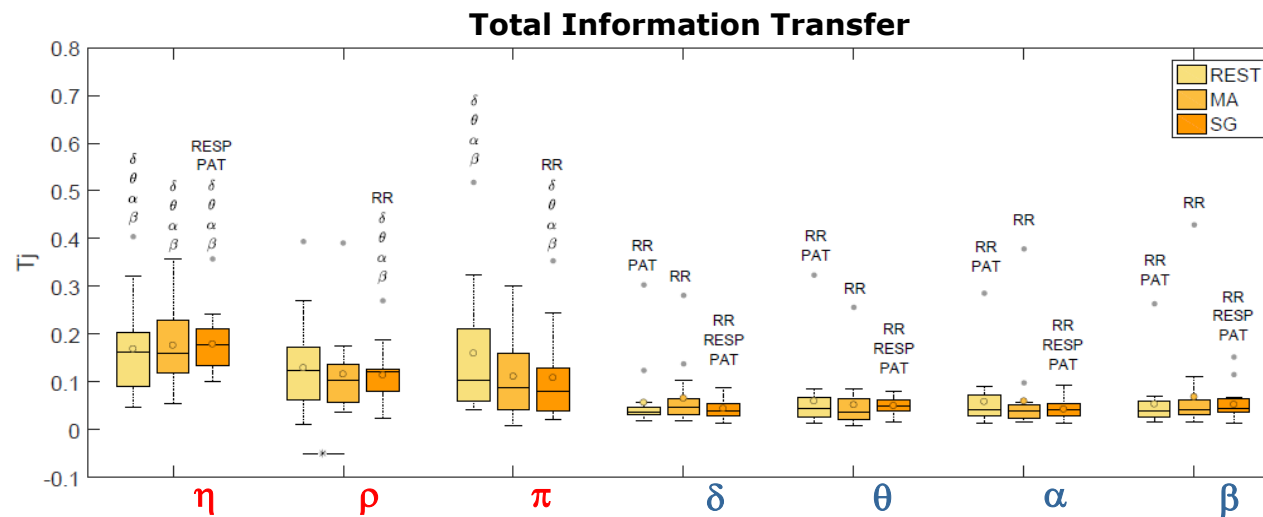


Brain-body interactions during stress: RESULTS

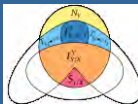
- Dynamic analysis: Information storage and total information transfer



- each node of the brain-body network stores and receives a statistically significant amount of information

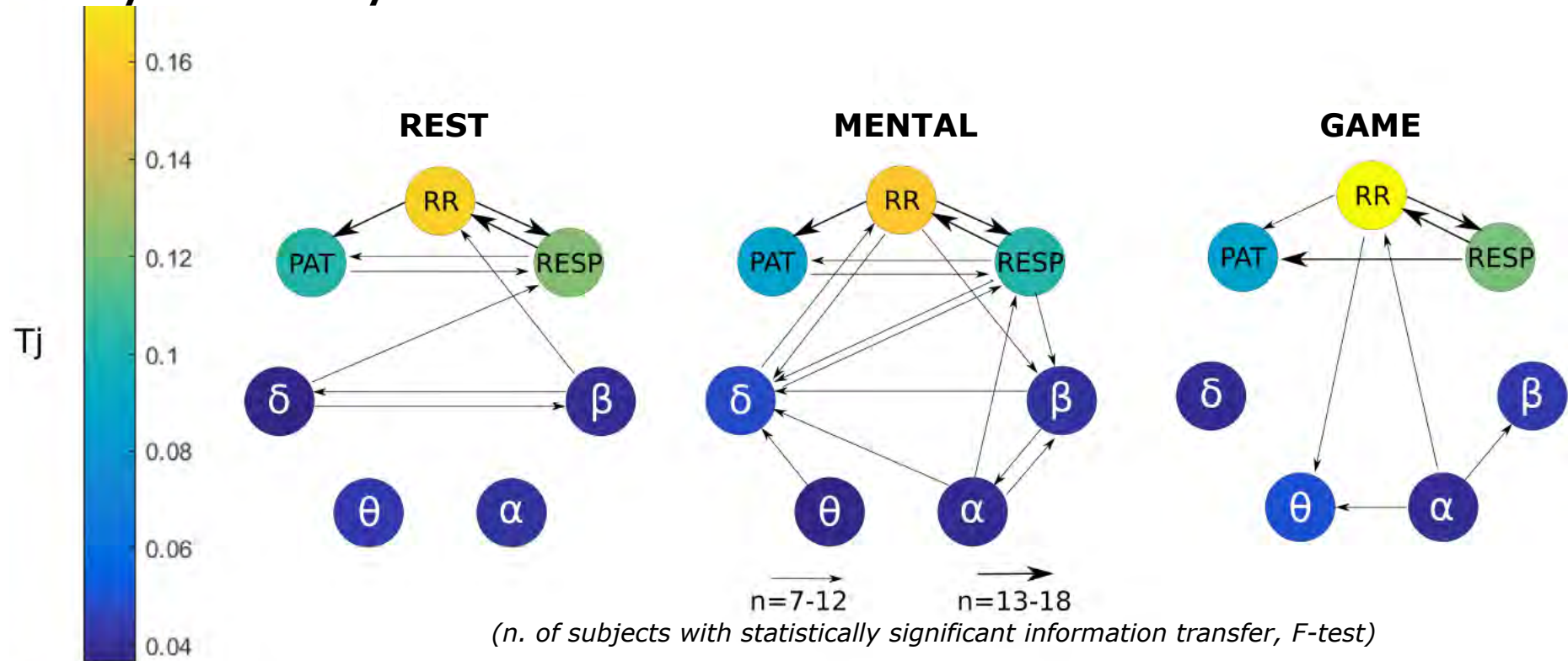


- Information storage and transfer are significantly higher for the heart, respiratory and cardiac nodes than for the four brain nodes

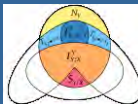


Brain-body interactions during stress: RESULTS

• Dynamical analysis: Conditional information transfer

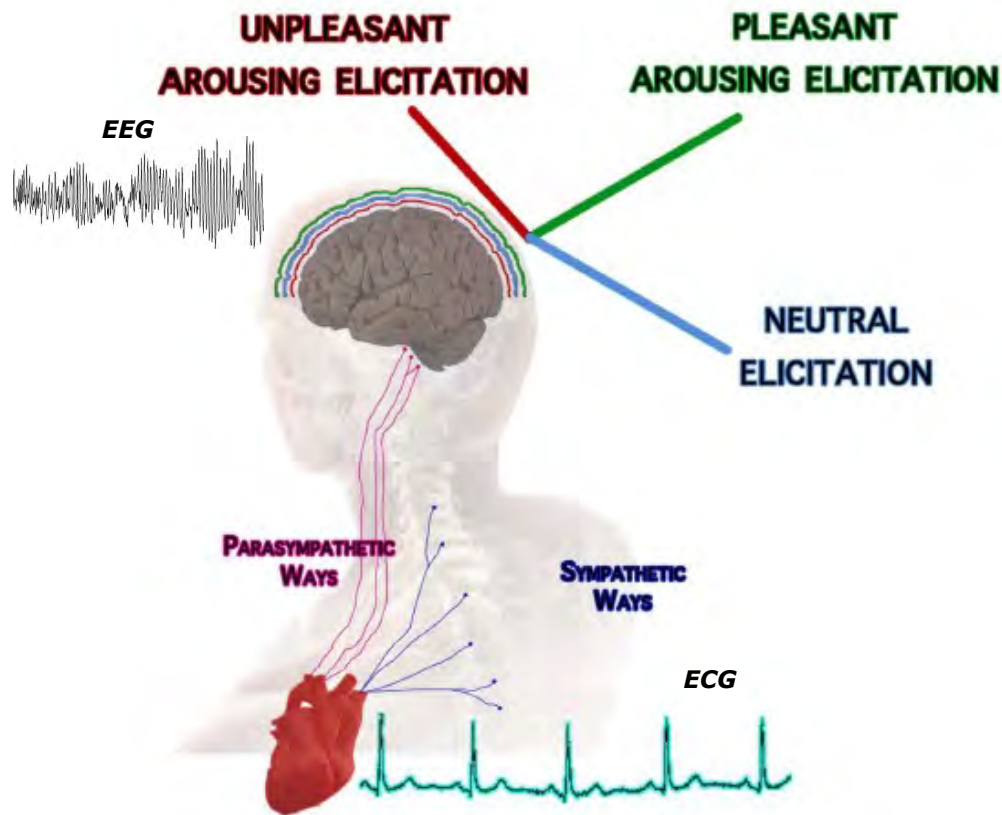


- *the body subnetwork is highly connected through cardiovascular and cardiorespiratory interactions*
- *the number of connections between brain and body increases during mental stress and decreases during sustained*



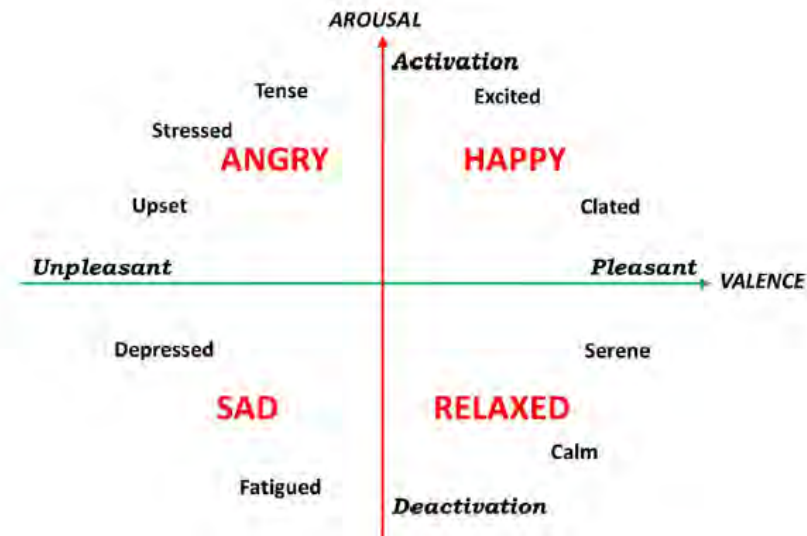
(3) BRAIN-HEART INTERACTIONS DURING EMOTION ELICITATION

- **Rationale:** ANS and CNS are connected anatomically and functionally, and such interaction plays a role during emotional experiences



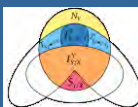
ANS – CNS interaction can be probed from simultaneous EEG-ECG recordings during affective elicitation

Circumplex Model of Affects:



[Posner, J et al, Dev. Psychopathol. 17, 2005]

- **AROUSAL:** how strongly the stimulus is felt
- **VALENCE:** how much the stimulus is perceived as positive or negative

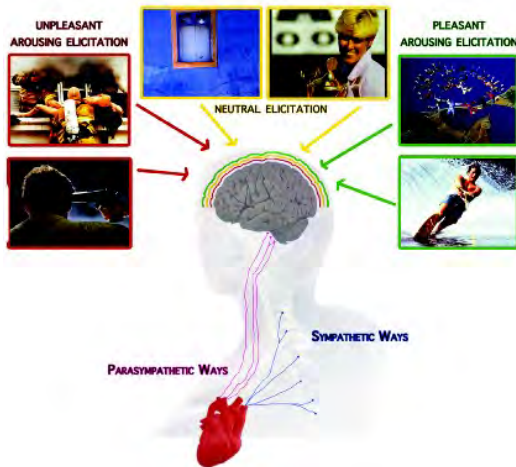


Brain-heart interactions during emotion elicitation: METHODS

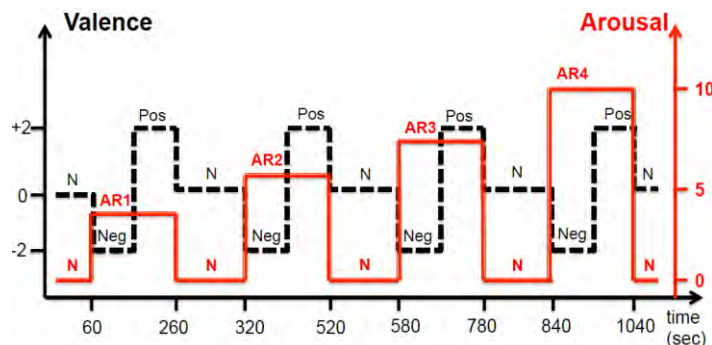
• Protocol: evoking emotions with different degrees of valence and arousal

✓ 22 healthy subjects (21-24 years old)

✓ Experimental protocol:



P. Lang, M. Bradley, and B. Cuthbert,
"International affective picture system 2005."



✓ Signals and time series:



• ECG → mean heart rate (μ), high-frequency component of HRV (HF)

[Barbieri et al. American Journal of Physiology 2005]

• EEG → spectral power in θ , α , β , γ bands

[P. Welch, IEEE Trans Audio Electroacoustics 1967]

✓ Experimental conditions:

- Rest (R)
- Neutral Elicitation (N)
- Arousal with positive valence (ARP)
- Arousal with negative valence (ARN)

✓ NETWORK REPRESENTATION: $N = \{S_1, \dots, S_6\} = \{X, Y\}$

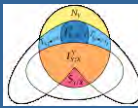
$$X = \begin{cases} \eta_{\mu} & \text{sympathetic + parasympathetic} \\ \eta_{HF} & \text{parasympathetic} \end{cases}$$

$$Y = \{\theta, \alpha, \beta, \gamma\}$$

Linear estimation of the Information Transfer:

$$T_{Y \rightarrow \eta} = I(\eta_n; Y_n^- | \eta_n^-) \quad , \quad \eta \in \{\eta_{\mu}, \eta_{HF}\}$$

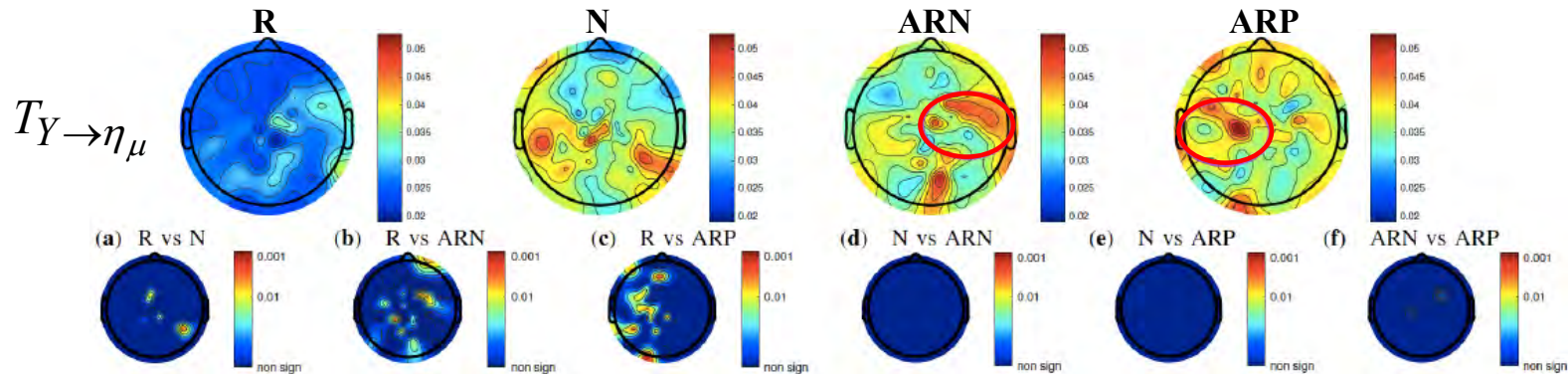
$$T_{\eta \rightarrow Y_i} = I(Y_{i,n}; \eta_n^- | Y_{i,n}^-) \quad , \quad Y_i \in \{\theta, \alpha, \beta, \gamma\}$$



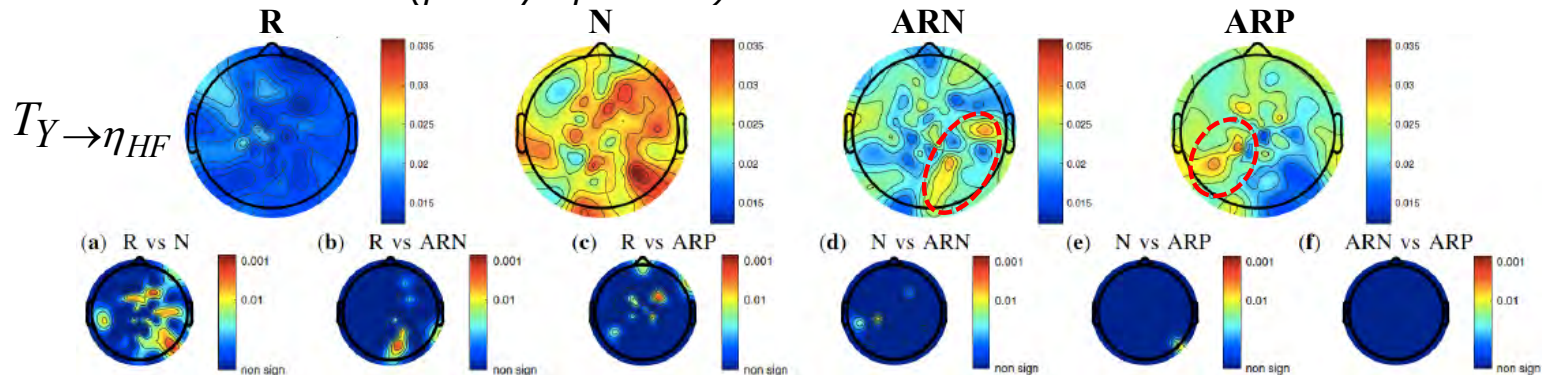
Brain-heart interactions during emotion elicitation: RESULTS

• Efferent information transfer: BRAIN → HEART

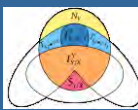
Transfer brain→heart μ (sympathetic+parasympathetic)



Transfer brain→heart HF (parasympathetic)



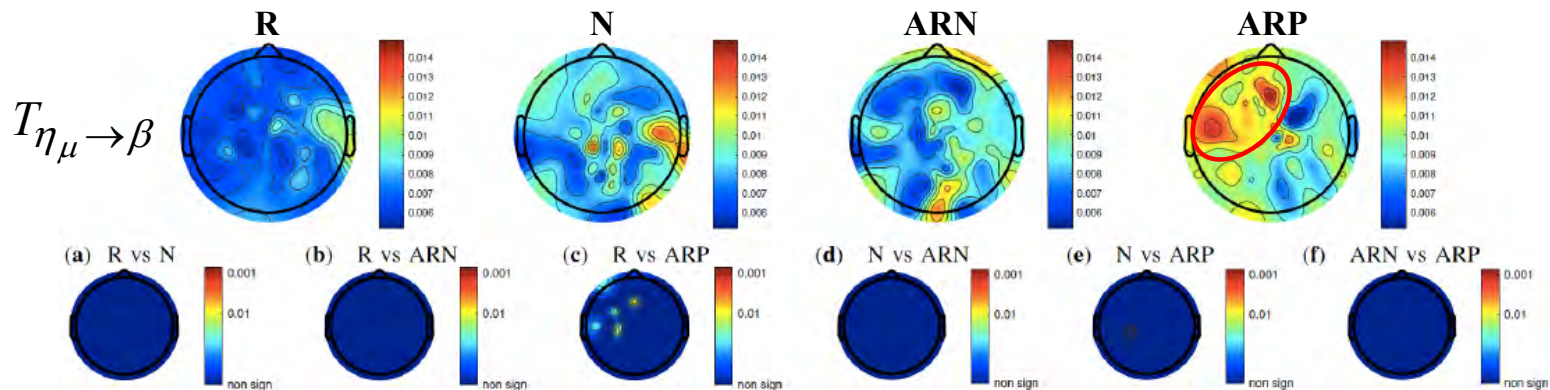
- **The brain→heart information transfer increases significantly during emotion elicitation**
- **Valence-dependent lateralization: higher left brain→heart transfer during positive elicitation**
higher right brain→heart transfer during negative elicitation



Brain-heart interactions during emotion elicitation: RESULTS

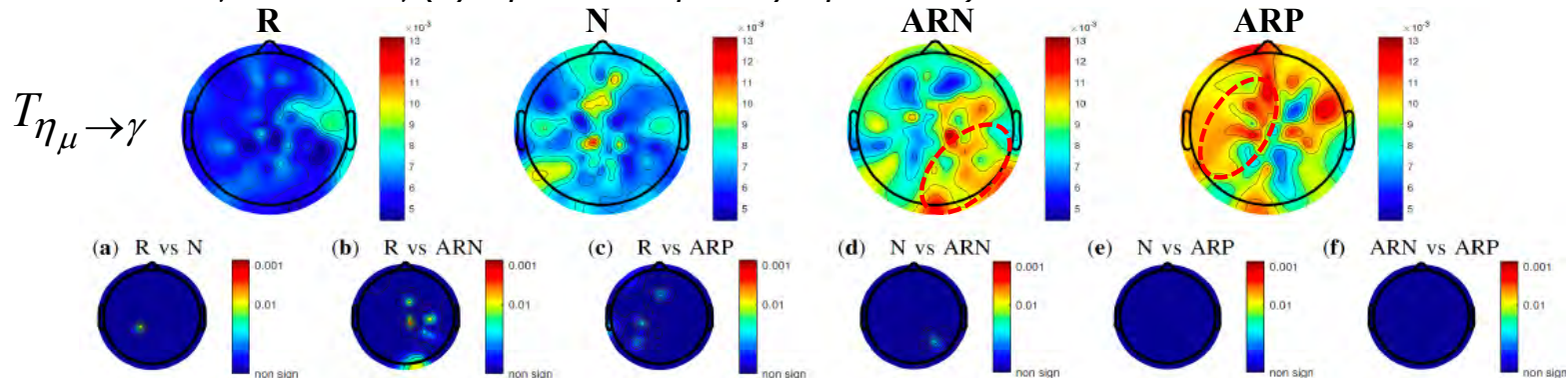
• Afferent information transfer: HEART → BRAIN

Transfer heart $\mu \rightarrow$ brain β (sympathetic+parasympathetic)

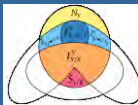


- Increased information transfer from heart to left frontal and somatosensory regions during positive elicitation

Transfer heart $\mu \rightarrow$ brain γ (sympathetic+parasympathetic)



- Valence-dependent lateralization: higher left heart→brain transfer during positive elicitation
higher right heart→brain transfer during negative elicitation



BRAIN-HEART INTERACTIONS IN TEMPORAL LOBE EPILEPSY

- Epileptic seizures influence both the cortical activity and the activity of the autonomic nervous system

- The separate study of the brain rhythms and of the cardiac dynamics underlying epilepsy has been performed for clinical purposes

[O.M. Doyle et al., Med. Eng. Phys. 32, 2010]

[B. Moseley et al., Epilepsy Behav. 26, 2013]

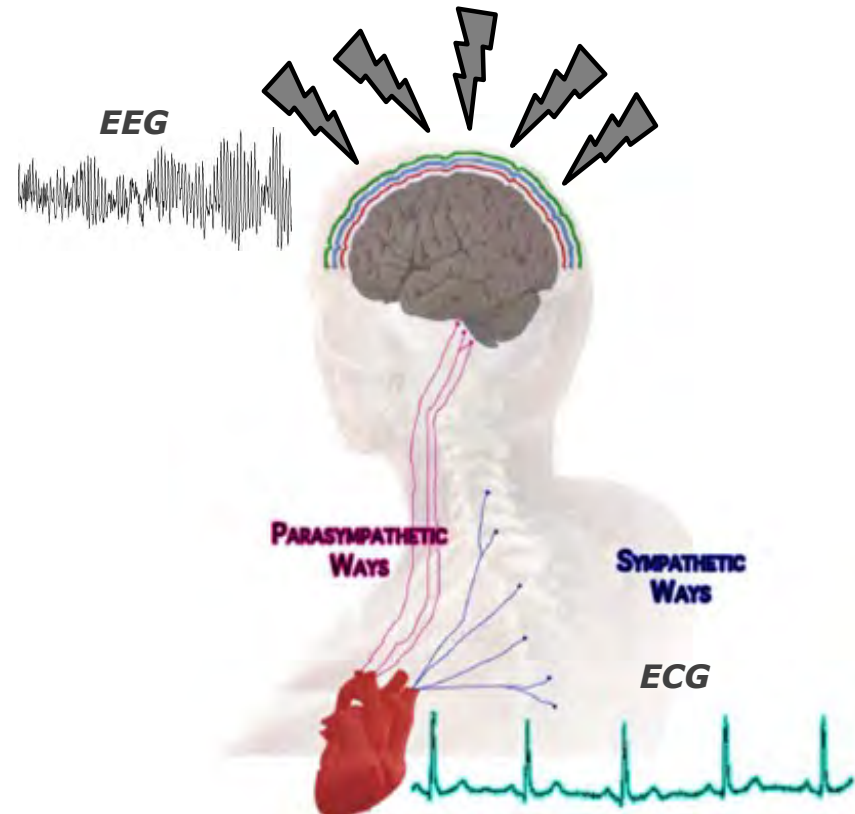
[C. Varon et al., Physiol. Meas. 36, 2015]

- Recent works studied the correlation between the epileptic neural network and the autonomic nervous system

[D. Piper et al., New J. Phys. 16, 2014]

[K. Schiecke et al., IEEE Trans. Biomed Eng. 63, 2016]

- **AIM:** investigating the potential of information dynamics to reveal brain-heart interactions before, during and after epileptic discharges in children with temporal lobe epilepsy

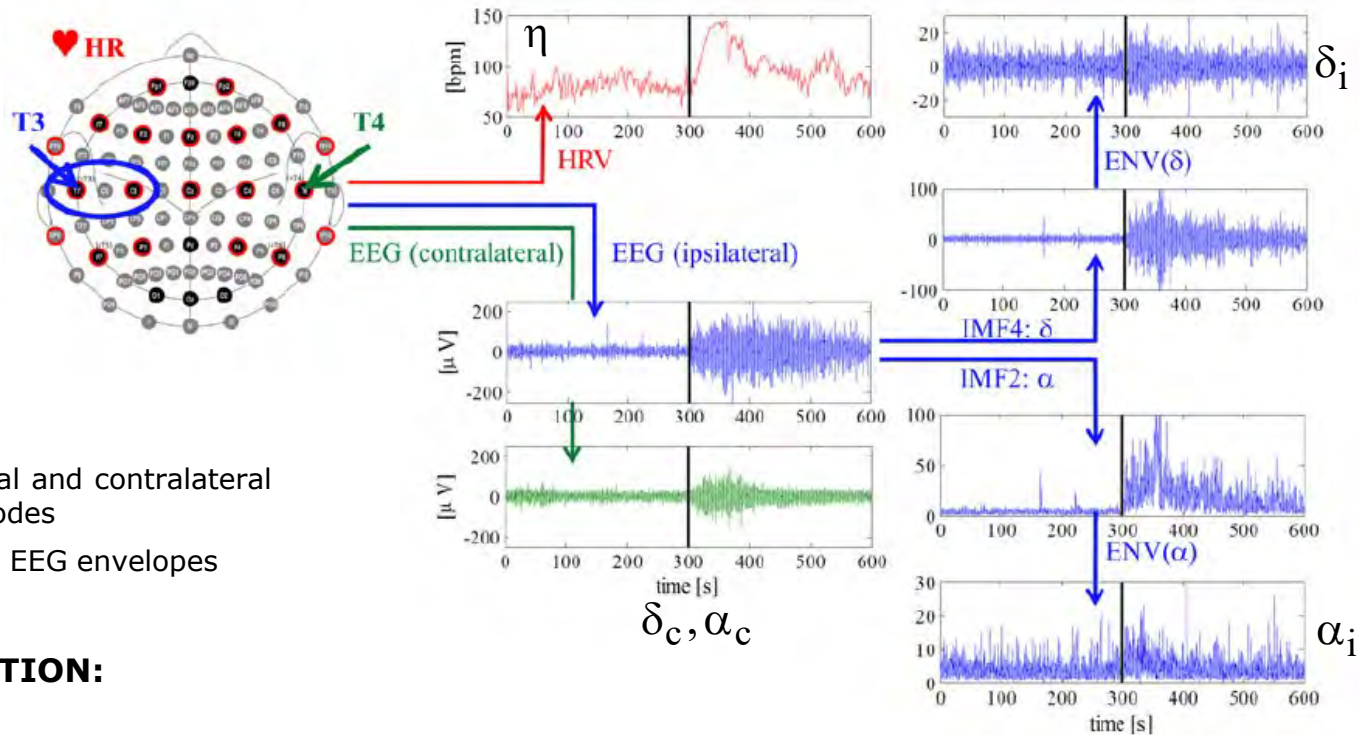




Brain-heart interactions in epilepsy: METHODS

• PROTOCOL:

- ✓ 22 children with **temporal lobe epilepsy**
- ✓ **Pre-ictal** (5 min)
- ✓ **Ictal** (~ 1.5 min)
- ✓ **Post-ictal** (~ 4.5 min)
- ✓ ECG → HRV
- ✓ EEG: • Selection of ipsilateral and contralateral temporal lobe electrodes
• Extraction of δ and α EEG envelopes



• NETWORK REPRESENTATION:

$$N = \{S_1, \dots, S_5\} = \{X, Y\}$$

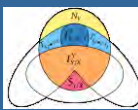
$$X = \eta, Y = \{\delta_i, \delta_c, \alpha_i, \alpha_c\}$$

- Information Transfer (linear estimates): *brain* → *heart*: $T_{\delta \rightarrow \eta} = I(\eta_n; \delta_n^- | \eta_n^-)$, $T_{\eta \rightarrow \delta} = I(\delta_n; \eta_n^- | \delta_n^-)$
heart → *brain*: $T_{\alpha \rightarrow \eta} = I(\eta_n; \alpha_n^- | \eta_n^-)$, $T_{\eta \rightarrow \alpha} = I(\alpha_n; \eta_n^- | \alpha_n^-)$

- Partial information decomposition of brain→heart interactions:

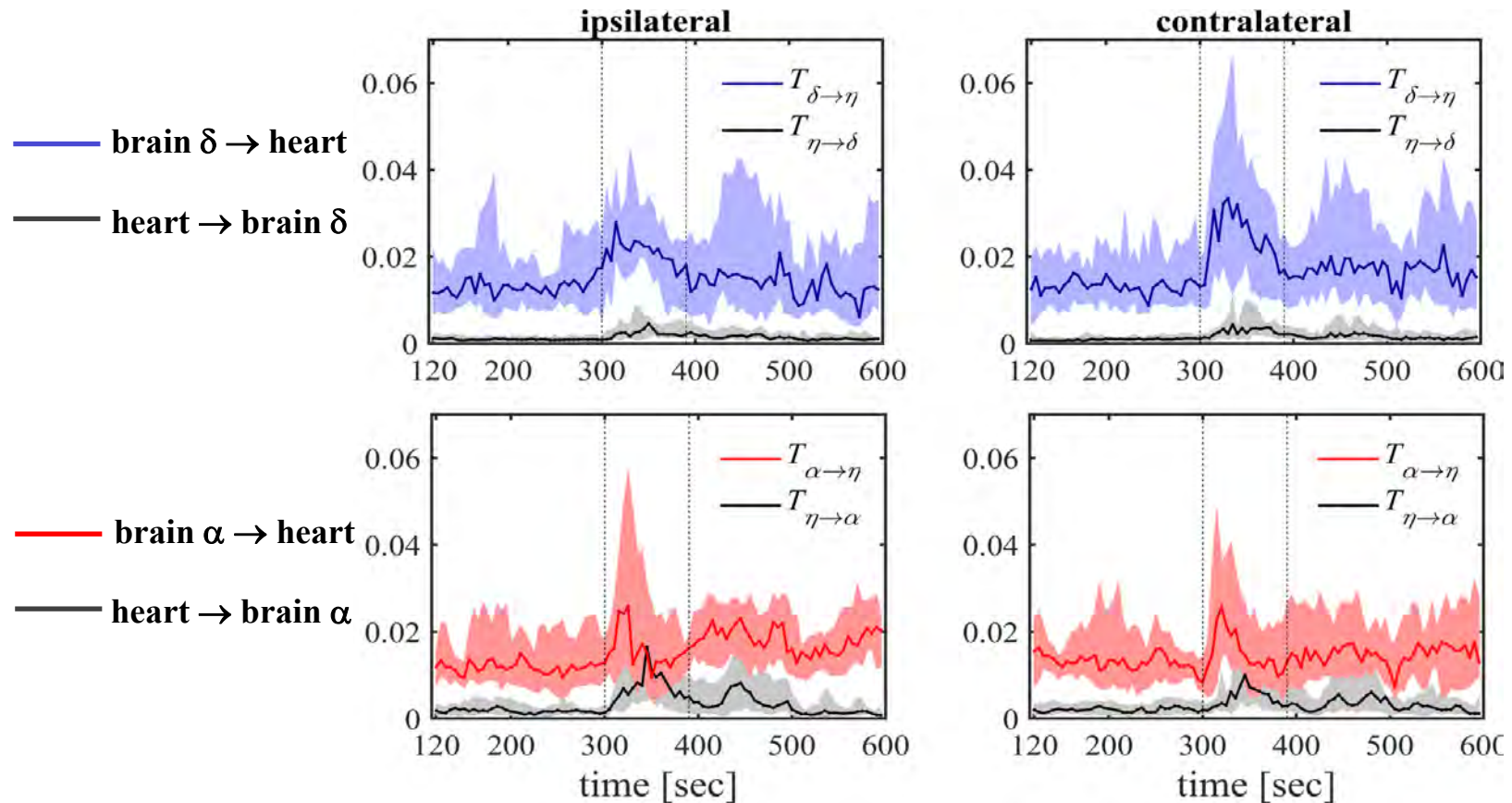
$$T_{\delta_i, \delta_c \rightarrow \eta} = U_{\delta_i \rightarrow \eta} + U_{\delta_c \rightarrow \eta} + R_{\delta_i; \delta_c}^\eta + S_{\delta_i; \delta_c}^\eta$$

$$T_{\alpha_i, \alpha_c \rightarrow \eta} = U_{\alpha_i \rightarrow \eta} + U_{\alpha_c \rightarrow \eta} + R_{\alpha_i; \alpha_c}^\eta + S_{\alpha_i; \alpha_c}^\eta$$



Brain-heart interactions in epilepsy: RESULTS

• Brain-Heart Information Transfer

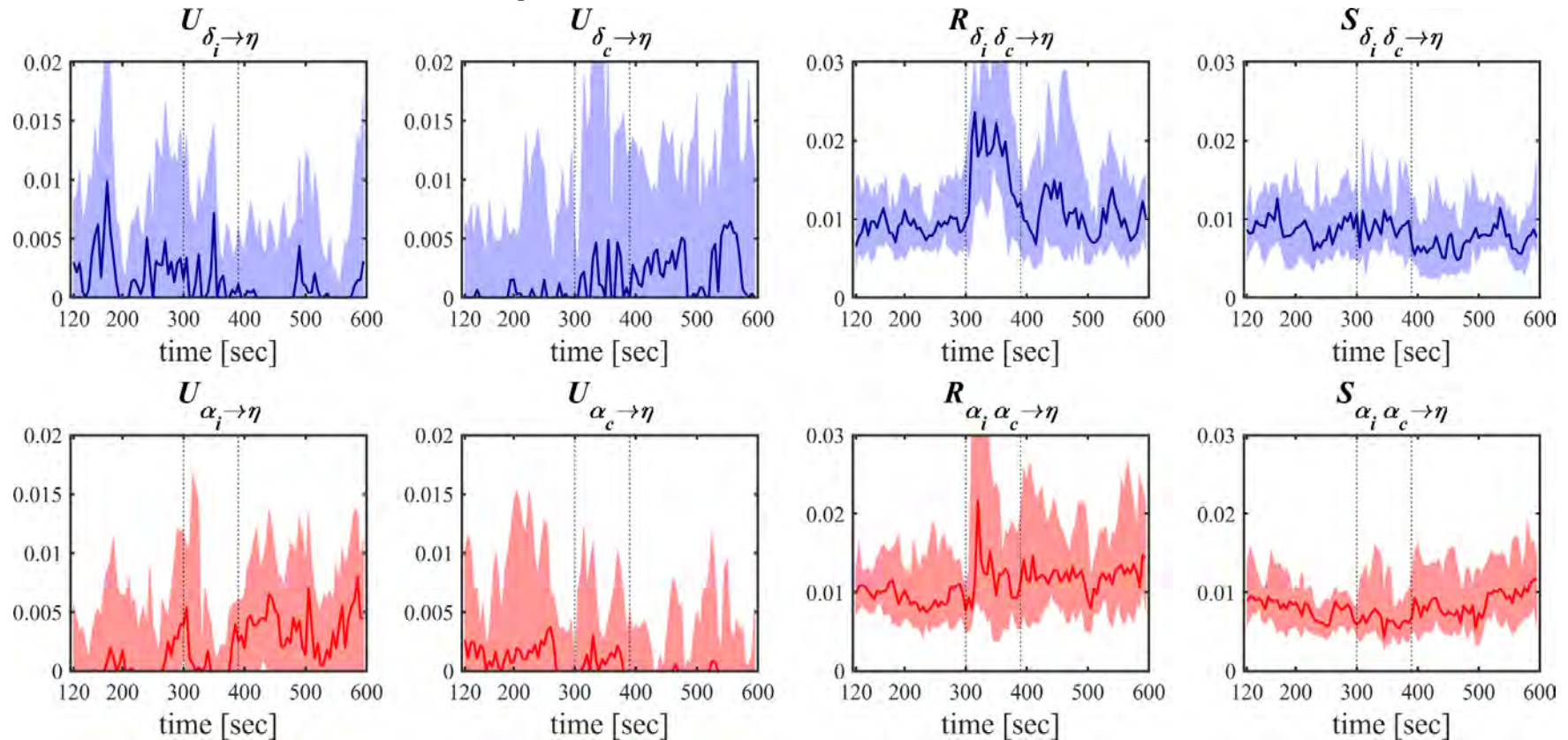


- *The information transfer is markedly higher along the brain \rightarrow heart direction*
- *No evident differences are observed between δ and α waves, pre-ictal and post-ictal phases, or contralateral and ipsilateral sites*

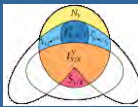


Brain-heart interactions in epilepsy: RESULTS

• Partial information decomposition of brain→heart information transfer



- *The unique information transfer $\delta \rightarrow \eta$ is mostly ipsilateral in the pre-ictal phase and contralateral during the seizure and in the post-ictal phase*
- *These findings document the importance of PID, which removes from the information transfer the redundancy between the EEG activity of the two hemispheres*



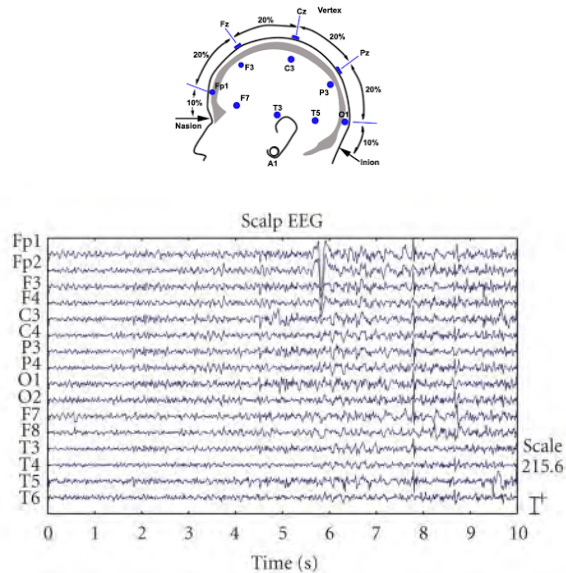
APPLICATIONS: SINGLE ORGAN NETWORKS

- Brain Networks from EEG recordings
- Muscle Networks probed during postural control

Study of networks formed by multichannel acquisitions of the same biomedical signal

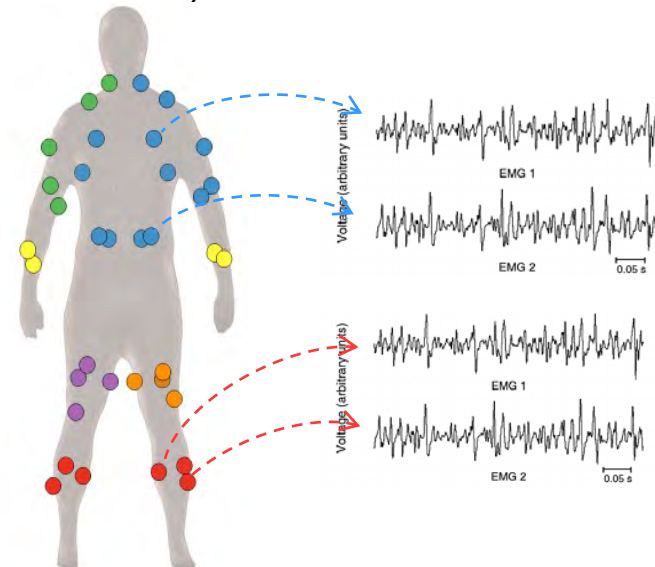
- **Brain Networks**

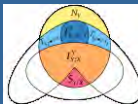
Multichannel scalp EEG



- **Muscular Networks**

Whole body multichannel EMG

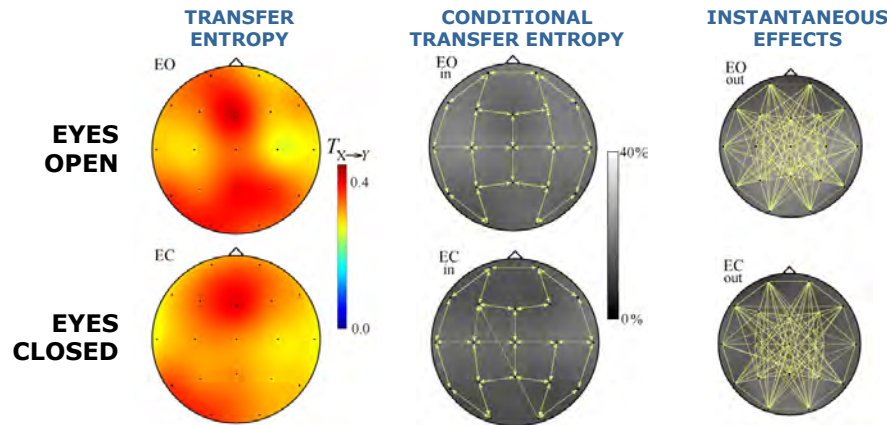
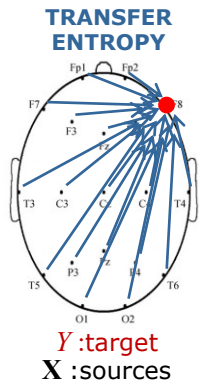




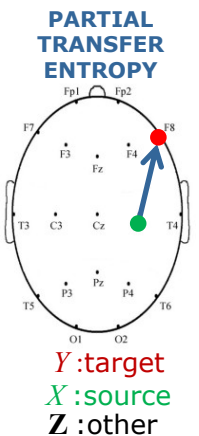
Information Dynamics of Scalp EEG Networks

- Protocol: scalp EEG in 21 healthy subjects during eyes open and eyes closed
- Nearest neighbor estimate of information transfer and conditional information transfer between all sensors

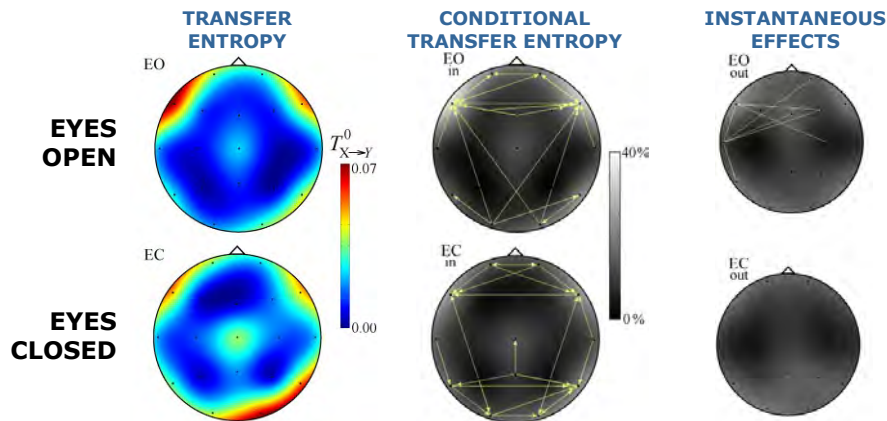
Classical measures



- Uniform Information transfer
- Dense connectivity between adjacent sensors
- Instantaneous dependencies between all sensors
- Patterns unchanged between conditions



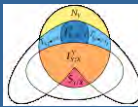
Compensated measures



- Abolishment of instantaneous correlations
- Emergence of patterns of causal connectivity

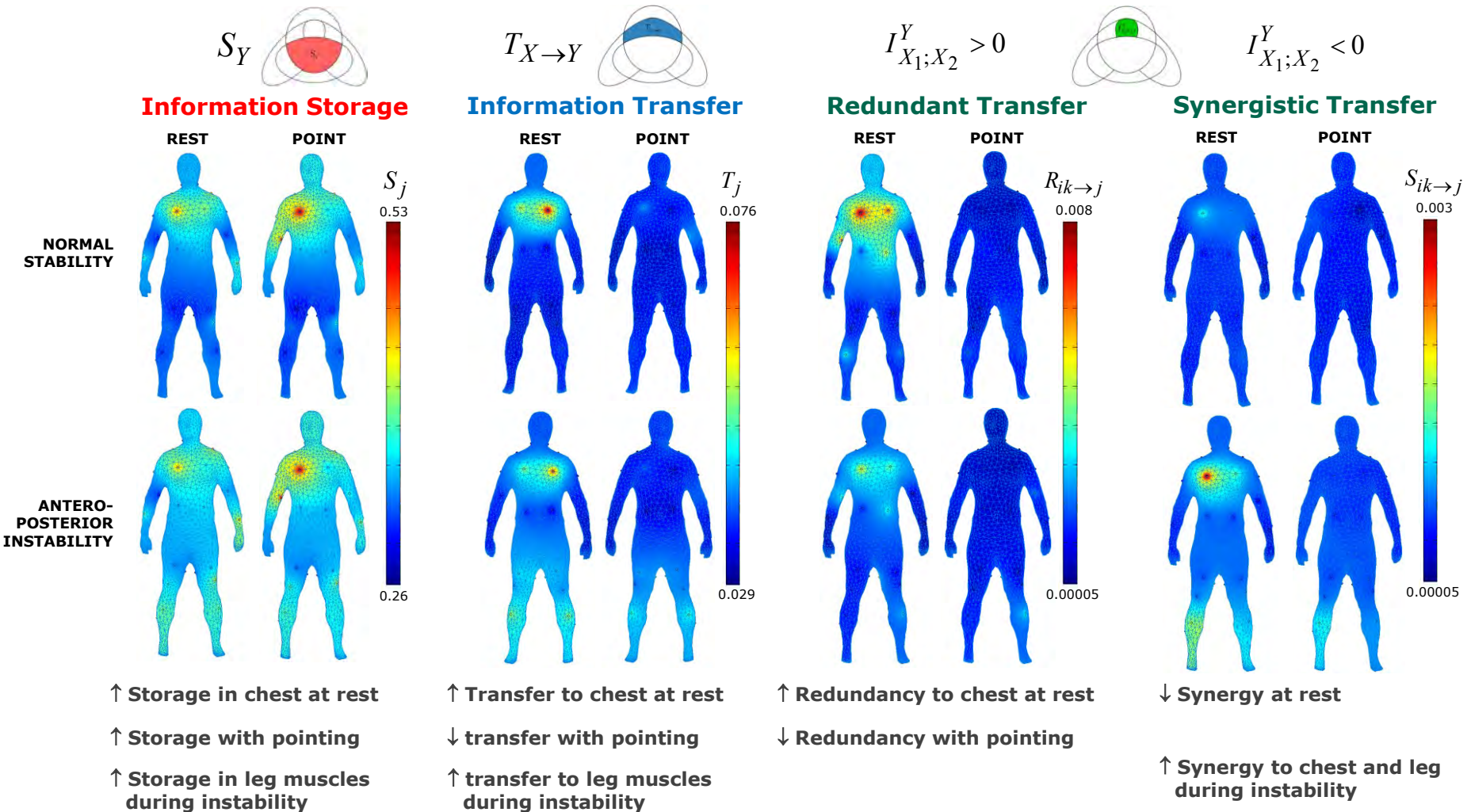
Local sinks of information flow:

- anterior during EO
- anterior + occipital during EC



Information Dynamics of Muscle Networks

- Protocol: multichannel EMG in 14 healthy subjects
- Conditions: standing and pointing to a target during normal altered stability



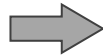


“The human organism is an integrated network where complex physiologic systems, each with its own regulatory mechanisms, continuously interact, and where failure of one system can trigger a breakdown of the entire network”

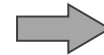
[A. Bashan et al., Nature Communications 2012]

*A new field, **Network Physiology**, is needed to probe the interactions among diverse physiologic systems*

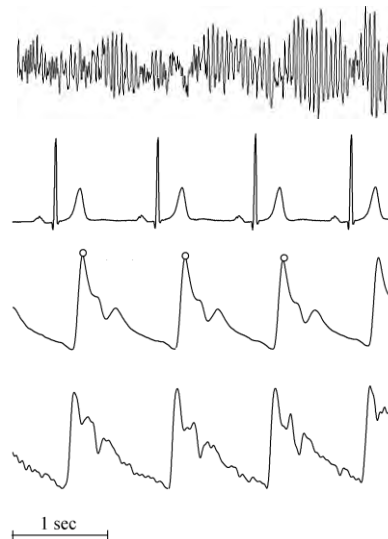
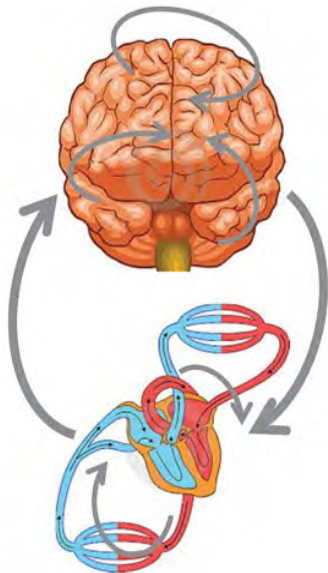
SYSTEMS



SIGNALS



INFORMATION DYNAMICS



Information Storage

Information Transfer

Information Modification

